

Editorial

Introduction to ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

This supplement of *Pediatric Diabetes* is an update of the guideline chapters that were originally individually published in the journal between 2006 and 2008, and as a single compendium edition in 2009. The chapters have been modified and updated to reflect the significant advances in scientific knowledge and clinical care that have occurred since then. These updated guidelines also are available on the International Society for Pediatric and Adolescent Diabetes (ISPAD) website: www.ispad.org.

In 2007, the total child population of the world (0–14 yr) was estimated to be 1.8 billion, of whom 0.02% had diabetes. This means that approximately 497 000 children around the world have diabetes, with 79 000 new cases diagnosed each year (1). However, field data suggest that some individual country estimates (especially in developing countries) are uncertain or inaccurate. These very large numbers of children need help to survive with insulin injections in order to live a full life without restrictions or disabling complications and without being stigmatized for their diabetes.

Even today, almost a century after the discovery of insulin, the most common cause of death in a child with diabetes from a global perspective is a lack of access to insulin (2). Many children die before their diabetes is diagnosed. It is therefore of utmost importance that all forces unite to make it come true that no child should die from diabetes. A promising initiative has been taken by the International Diabetes Federation (IDF) ‘Life for a Child’ programme (www.lifeforachild.org) in collaboration with ISPAD and other organizations. Several major companies that produce insulin and other diabetes-related products have pledged their support, and the number of children and youth provided with insulin, test strips, and other support is around 13 000 in 2014 and will continue to increase. Currently 46 countries are involved. ISPAD has also pledged support and assistance in the training of pediatricians and health care professionals in childhood and adolescent diabetes through its membership network. CDiC (Changing Diabetes in Children) is another initiative providing insulin and

diabetes care to India, Bangladesh, and a number of countries in Africa. Additional initiatives by ISPAD to improve diabetes care for children and adolescents worldwide include its ‘science schools’ for physicians and for other health care professions, its postgraduate courses and its Diabetes in Practice (DIP) programme, which have been held in a number of countries around the world. ISPAD also provides tutoring in collaboration with the European Society for Pediatric Endocrinology (ESPE) at Pediatric Endocrine and Diabetes Training Center in Africa (PETCA) in Nairobi and at Pediatric Endocrine and Diabetes Training Center in West Africa (PETCWA) in Lagos for fellows from Africa in pediatric diabetology and endocrinology.

In 1993, members of the ISPAD formulated the Declaration of Kos, proclaiming their commitment to ‘promote optimal health, social welfare, and quality of life for all children with diabetes around the world by the year 2000’. Although all the aims and ideals of the Declaration of Kos were not reached by 2000, we feel that slowly, by small steps, the worldwide care of children with diabetes is improving.

ISPAD published its first set of guidelines in 1995 (3), its second in 2000 (4), and its third in 2009 (5). Since then, the acceptance of intensive therapy, also for very young children, has increased around the world. Insulin pump usage has risen in all age groups in countries where this treatment modality can be afforded. Intensive therapy requires better and more comprehensive education for it to be successful.

The ISPAD Consensus Guidelines 2000 was translated into 11 languages, reflecting the need for a truly international document. In 2003–2005, national guidelines for childhood diabetes were released: the Australian Clinical Practice Guidelines from the National Health and Medical Research Council (5), and in the UK, the National Institute for Clinical Excellence (NICE) Clinical Guideline (6). Both these publications were truly evidence-based in that they deal with the body of evidence with a systematic approach, grading each reference and building the case for each recommendation. In 2003, the Canadian Diabetes

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Association published Clinical Practice Guidelines with chapters both on type 1 and type 2 diabetes in children and adolescents (7). In 2005, the American Diabetes Association (ADA) published its statement on the care of children and adolescents with type 1 diabetes (8) which has recently been updated and now shares the ISPAD hemoglobin A1c (HbA1c) target of <7.5% for all children and adolescents (9). ISPAD in collaboration with IDF has also produced the Global IDF/ISPAD Guideline for Diabetes in Childhood and Adolescence, introducing three levels of care: recommended care, comprehensive care, and limited care. In this edition of the ISPAD Guidelines, a 'limited care' section can also be found in the Supporting information.

This fourth edition of ISPAD's 'Clinical Practice Consensus Guidelines' is much larger, and has been enriched by the national guidelines mentioned above. All chapters are organized as follows: executive summary and recommendations, supporting body of the chapter, references, and as an appendix for limited care. As in past ISPAD guidelines, we have used the ADA system for grading evidence (noted below) (11). Whenever possible the reference for a statement or recommendation has been included, but as the reader will see, a vast majority of the recommendations and suggestions are graded as 'E', as they are solely based on expert consensus or clinical experience.

The ISPAD guidelines serve a critical function to gather in one document comprehensive advice on diabetes care that is not only focused on children and young people, but is also based on the latest evidence and on a wide consensus of clinical practice. They are also intended for worldwide application and have thus been drafted by international writing teams, modified by experts in different specialties from many countries and were posted for review by members via the ISPAD website. As far as possible, significant input by individuals has been acknowledged. The Editors wish to give their many thanks to the large number of individuals who have contributed but whose names could not be included.

The 2014 guidelines, as with previous editions, place patient, family, and health care provider education at the center of clinical management. Education is the vehicle for optimal self-management, the key to success.

We hope therefore that the guidelines will be widely consulted and will be used to:

- improve awareness among governments, state health care providers, and the general public of the serious long-term implications of poorly managed diabetes and of the essential resources needed for optimal care;

- assist individual care givers in managing children and adolescents with diabetes in a prompt, safe, consistent, equitable, standardized manner in accordance with the current views of experts in the field; and
- provide evidence-based advice to improve the care of children with diabetes.

As in 2009, 'these guidelines are not strict protocols nor are they the final word'. Individual clinical judgment and decision making also require the family's values and expectations to be considered with the best outcomes being reached by consensus.

The American Diabetes Association evidence grading system for clinical practice recommendations is as follows:

Level of evidence	Description
A	Clear evidence from well-conducted, generalizable, randomized, controlled trials that are adequately powered, including: <ul style="list-style-type: none">• Multicenter trial• Meta-analysis incorporating quality ratings• Compelling non-experimental evidence (i.e., 'all-or-none' rule) developed by the Center for Evidence-Based Medicine at Oxford^f Supportive evidence from well-conducted, randomized, controlled trials that are adequately powered, including: <ul style="list-style-type: none">• Well-conducted trials at ≥ 1 institutions
B	Supportive evidence from well-conducted cohort studies including: <ul style="list-style-type: none">• Prospective cohort studies or registry• Meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study.
C	Supportive evidence from poorly controlled or uncontrolled studies including: <ul style="list-style-type: none">• Randomized clinical trials with one major or three minor methodological flaws that could invalidate the results• Observational studies with high potential for bias• Case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation.
E	Expert consensus or clinical experience.

^fEither all patients died before therapy and at least some survived with therapy or some patients died without therapy and none died with therapy (e.g., the use of insulin in the treatment of diabetes ketoacidosis).

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Definition, epidemiology, and classification of diabetes in children and adolescents

Craig ME, Jefferies C, Dabelea D, Balde N, Seth A, Donaghue KC. Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatric Diabetes* 2014; 15 (Suppl. 20): 4–17.

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- Diagnostic criteria for diabetes are based on laboratory measurement of plasma glucose concentrations and the presence or absence of symptoms (E). Finger prick blood glucose level (BGL) testing should not be used to diagnose diabetes (E).
- A marked elevation of the blood glucose level confirms the diagnosis. If ketones are present in blood or urine, treatment is urgent, and the child should be referred the same day to avoid the development of ketoacidosis (A).
- The diagnosis of diabetes should not be based on a single plasma glucose concentration. If the diagnosis is in doubt, continued observation with fasting and/or 2 h postprandial blood glucose levels and/or an oral glucose tolerance test (OGTT) may be required (E). However, an OGTT is not needed and should not be performed if diabetes can be diagnosed using fasting, random, or postprandial criteria as excessive hyperglycemia can result (E).
- Hyperglycemia detected under conditions of stress, such as acute infection, trauma, surgery, respiratory distress, circulatory, or other stress may be transitory and requires treatment but should not in itself be regarded as diagnostic of diabetes (E).
- The possibility of other types of diabetes should be considered in the child who has negative diabetes-associated autoantibodies and (B):
 - An autosomal dominant family history of diabetes.
 - Diabetes diagnosed in the first 6 months of life.
 - Mild fasting hyperglycemia [5.5–8.5 mmol (100–150 mg/dL)], which does not progress, especially if young, non-obese, and asymptomatic.
 - Associated conditions such as deafness, optic atrophy, or syndromic features.
 - A history of exposure to drugs known to be toxic to β cells or cause insulin resistance.
- The differentiation between type 1, type 2, monogenic, and other forms of diabetes has important implications for both treatment and

education (E). Diagnostic tools, which may assist in confirming the diabetes type if the diagnosis is unclear, include:

- Diabetes-associated autoantibodies: Glutamic acid decarboxylase 65 autoantibodies (GAD); tyrosine phosphatase-like insulinoma antigen 2 (IA2); insulin autoantibodies (IAA); and β -cell-specific zinc transporter 8 autoantibodies (ZnT8). The presence of one or more of these antibodies confirms the diagnosis of type 1 diabetes (A).
- OGTT (A).
- Haemoglobin A1c (HbA1c) (B).
- Molecular genetic testing can help define the diagnosis and treatment of children with suspected monogenic diabetes. All patients diagnosed with diabetes in the first 6 months of life should have immediate molecular genetic testing to define their subtype of neonatal diabetes mellitus (NDM), as type 1 diabetes is extremely rare in this subgroup (B). Beyond the age of 6 months, genetic testing should be limited to those with negative autoantibodies (particularly if measured at diagnosis), who have clinical features suggestive of monogenic diabetes who on clinical grounds are likely to be positive (E).

Definition and description

The term diabetes mellitus describes a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Inadequate insulin secretion and/or diminished tissue responses to insulin in the complex pathways of hormone action result in deficient insulin action on target tissues, which leads to abnormalities of carbohydrate, fat, and protein metabolism. Impaired insulin secretion and/or action may coexist in the same patient (1, 2).

While the etiology of diabetes is heterogeneous, most cases of diabetes can be classified into two broad etiopathogenetic categories (discussed in further detail below): type 1 diabetes, which is characterized by an absolute deficiency of insulin secretion; or type 2 diabetes, which results from a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. While type 1 diabetes remains the most common form of diabetes in young people in many populations, especially those of Caucasian background, type 2 diabetes has become an increasingly important public health concern globally, see the ISPAD guideline on type 2 diabetes (3).

Definition, epidemiology, and classification of diabetes

Diagnostic criteria for diabetes in childhood and adolescence

Diagnostic criteria for diabetes are based on blood glucose measurements and the presence or absence of symptoms (1, 4). Different methods can be used to diagnose diabetes (Table 1) and in the absence of unequivocal hyperglycemia, must be confirmed by repeat testing.

- Diabetes in young people usually presents with characteristic symptoms such as polyuria, polydipsia, nocturia, enuresis, weight loss – which may be accompanied by polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia.
- In its most severe form, ketoacidosis or less commonly non-ketotic hyperosmolar syndrome may develop and lead to stupor, coma and in the absence of effective treatment, death.
- If symptoms are present, urinary ‘dipstick’ testing for glycosuria and ketonuria, or measurement of glucose and ketones using a bedside glucometer, provides a simple and sensitive screening tool. If the blood glucose level is elevated, then prompt referral to a center with experience in managing children with diabetes is essential. Waiting another day specifically to confirm the hyperglycemia is unnecessary and if

Table 1. Criteria for the diagnosis of diabetes mellitus (1, 2)

- | | |
|-----|--|
| i | Classic symptoms of diabetes or hyperglycemic crisis, with plasma glucose concentration ≥ 11.1 mmol/L (200 mg/dL) or |
| ii | Fasting plasma glucose ≥ 7.0 mmol/L (≥ 126 mg/dL). Fasting is defined as no caloric intake for at least 8 h* or |
| iii | Two hour postload glucose ≥ 11.1 mmol/L (≥ 200 mg/dL) during an OGTT*. <ul style="list-style-type: none"> • The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g or |
| iv | HbA1c $> 6.5\%$ † <ul style="list-style-type: none"> • The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay |

HbA1c, hemoglobin A1c; OGTT, oral glucose tolerance test
*In the absence of unequivocal hyperglycemia, the diagnosis of diabetes based on these criteria should be confirmed by repeat testing.

†A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests. The role of HbA1c alone in diagnosing type 1 diabetes in children is unclear.

ketones are present in blood or urine, treatment is urgent, because ketoacidosis can evolve rapidly.

- A formal plasma glucose measurement is required to confirm the diagnosis; this should be based on laboratory glucose oxidase estimation rather than a capillary blood glucose monitor.
- Scenarios where the diagnosis of diabetes may be unclear include:
 - Absence of symptoms, for example, hyperglycemia detected incidentally or in children participating in screening studies
 - Presence of mild/atypical symptoms of diabetes
 - Hyperglycemia detected under conditions of acute infective, traumatic, circulatory, or other stress, which may be transitory and should not be regarded as diagnostic of diabetes.

In these situations, the diagnosis of diabetes should not be based on a single plasma glucose concentration and continued observation with fasting and 2 h postprandial blood glucose levels and/or an OGTT may be required to confirm the diagnosis.

- An OGTT is not required and should not be performed if diabetes can be diagnosed using fasting, random, or postprandial criteria as excessive hyperglycemia can result. It is rarely indicated in making the diagnosis of type 1 diabetes in childhood and adolescence, but may be useful in diagnosing other forms such as type 2 diabetes, monogenic diabetes, or cystic fibrosis related diabetes (CFRD). If doubt remains, periodic retesting should be undertaken until the diagnosis is established.
- HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement (2, 5). However, in rapidly evolving diabetes, such as the development of type 1 diabetes in some children, HbA1c may not be significantly elevated despite classic symptoms of diabetes.

Impaired glucose tolerance and impaired fasting glucose

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes (2). IFG and IGT are not interchangeable and represent different abnormalities of glucose regulation or different stages in the progression of dysglycemia. IFG is a measure of disturbed carbohydrate metabolism in the basal state while IGT is a dynamic measure of

carbohydrate intolerance after a standardized glucose load. IFG and IGT are not clinical entities in their own right; patients with IFG and/or IGT are referred to as having 'prediabetes' indicating their relatively high risk for development of diabetes and cardiovascular disease.

IFG and IGT may be associated with the metabolic syndrome, the features of which include obesity (particularly abdominal or visceral obesity), dyslipidemia [high triglyceride and/or low-high-density lipoprotein (HDL)], and hypertension. IFG and IGT can be observed as intermediate stages in any of the disease processes listed in Table 2 (etiologic classification of diabetes).

Individuals who meet criteria for IGT or IFG may be euglycemic in their daily lives as shown by normal or near-normal HbA1c, and those with IGT may manifest hyperglycemia only when challenged with an OGTT.

Categories of fasting plasma glucose (FPG) are defined as follows:

- FPG <5.6 mmol/L (100 mg/dL) = normal fasting glucose.
- FPG 5.6–6.9 mmol/L (100–125 mg/dL) = IFG.
- FPG ≥7.0 mmol/L (126 mg/dL) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described in Table 1).

The corresponding categories when the OGTT is used are as follows:

- Two hour postload glucose <7.8 mmol/L (140 mg/dL) = normal glucose tolerance.
- Two hour postload glucose 7.8–<11.1 mmol/L (140–200 mg/dL) = IGT.
- Two hour postload glucose ≥11.1 mmol/L (200 mg/dL) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above).

Classification of diabetes and other categories of glucose regulation

The type of diabetes assigned to a young person at diagnosis is typically based on their characteristics at presentation, however, increasingly the ability to make a clinical diagnosis has been hampered by factors including the increasing prevalence of overweight in young people with type 1 diabetes (6, 7) and the presence of diabetic ketoacidosis (DKA) in some young people at diagnosis of type 2 diabetes (8, 9). In addition, the presentation of a familial form of mild diabetes during adolescence should raise the suspicion of monogenic diabetes, which accounts for 1–4% of pediatric diabetes cases (10–13).

The etiological classification of diabetes is shown in Table 2, which is based on the American Diabetes

Table 2. Etiological classification of diabetes

I. Type 1

β-Cell destruction, usually leading to absolute insulin deficiency

- A. Immune mediated
- B. Idiopathic

II. Type 2

May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance

III. Other specific types

A. Genetic defects of β-cell function

- 1. Chromosome 12, *HNF1A* (MODY3)
- 2. Chromosome 7, *GCK* (MODY2)
- 3. Chromosome 20, *HNF4B* (MODY1)
- 4. Other rare forms of MODY including:
 - Chromosome 13, *IPF-1* (MODY4);
 - Chromosome 17, *HNF1B* (MODY5);
 - Chromosome 2, *NEUROD1* (MODY6);
 - Chromosome 2, *KLF11* (MODY7);
 - Chromosome 9, *CEL* (MODY8);
 - Chromosome 7, *PAX4* (MODY9)
- 5. TNDM (most commonly *PLAGL1/HYMAI* imprinting defect on 6q24)
- 6. PNDM (most commonly *KCNJ11* gene encoding Kir6.2 subunit of beta-cell KATP channel)
- 7. Mitochondrial DNA mutation
- 8. Others

B. Genetic defects in insulin action

- 1. Type A insulin resistance
- 2. Leprechaunism
- 3. Rabson–Mendenhall syndrome
- 4. Lipotrophic diabetes
- 5. Others

C. Diseases of the exocrine pancreas

- 1. Pancreatitis
- 2. Trauma/pancreatectomy
- 3. Neoplasia
- 4. Cystic fibrosis
- 5. Hemochromatosis
- 6. Fibrocalculous pancreatopathy
- 7. Others

D. Endocrinopathies

- 1. Acromegaly
- 2. Cushing's syndrome
- 3. Glucagonoma
- 4. Pheochromocytoma
- 5. Hyperthyroidism
- 6. Somatostatinoma
- 7. Aldosteronoma
- 8. Others

E. Drug- or chemical-induced

- 1. Vacor
- 2. Pentamidine
- 3. Nicotinic acid
- 4. Glucocorticoids
- 5. Thyroid hormone
- 6. Diazoxide
- 7. β-Adrenergic agonists
- 8. Thiazides
- 9. Dilantin
- 10. α-Interferon
- 11. Others

F. Infections

- 1. Congenital rubella
- 2. Cytomegalovirus
- 3. Enterovirus
- 4. Others

G. Uncommon forms of immune-mediated diabetes

- 1. 'Stiff-man' syndrome
- 2. Anti-insulin receptor antibodies
- 3. Autoimmune polyendocrine syndrome (APS) types I and II
- 4. IPEX
- 5. Others

H. Other genetic syndromes sometimes associated with diabetes

- 1. Down syndrome
- 2. Klinefelter syndrome
- 3. Turner syndrome
- 4. Wolfram syndrome
- 5. Friedreich's ataxia
- 6. Huntington's chorea
- 7. Laurence–Moon–Biedl syndrome
- 8. Myotonic dystrophy
- 9. Porphyria
- 10. Prader–Willi syndrome
- 11. Others

IV. Gestational diabetes mellitus (GDM)

CEL, carboxyl ester lipase; *HNF*, hepatocyte nuclear factor; *IPEX*, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; *IPF*, insulin promoter factor; *KLF11*, Kruppel-like factor 11; *MODY*, maturity-onset diabetes of the young; *PAX4*, Paired Domain gene 4.

Individuals with any form of diabetes may or may not require insulin treatment at various stages of their disease. Such use of insulin does not, of itself, classify the diabetes type.

Association classification (2). Some forms, including specific drug-, hormone-, or toxin-induced forms of diabetes, are rarely observed in young people. In Africa and South Asia, atypical forms of diabetes may occur in older children, adolescents, and young adults. These

include ketosis-prone atypical diabetes, malnutrition-related diabetes, and fibrocalculous pancreatic disease (14, 15).

The differentiation between type 1, type 2, monogenic, and other forms of diabetes has important

implications for both therapeutic decisions and educational approaches. Diagnostic tools, which may assist in confirming the diabetes type, include:

- Diabetes-associated autoantibodies: the presence of GAD, IA2, IAA, and/or ZnT8 confirms the diagnosis of type 1 diabetes, as one and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected (16).
- An elevated fasting C-peptide level can distinguish young people with non-autoimmune, insulin resistant type 2 diabetes from type 1 diabetes (17). However, as there is considerable overlap in insulin or C-peptide measurements between type 1 and type 2 diabetes in the first year after diagnosis, C-peptide measurements are not recommended in the acute phase. If patients are insulin treated, measuring C-peptide when the glucose is sufficiently high (>8 mmol/L) to stimulate C peptide will detect if endogenous insulin secretion is still present. This is rare beyond the remission phase (2–3 yr) in children with type 1 diabetes.

The possibility of other types of diabetes should be considered in the child who has no autoantibodies and:

- an autosomal dominant family history of diabetes;
- diabetes diagnosed in the first 6 months of life;
- mild fasting hyperglycemia [5.5–8.5 mmol (100–150 mg/dL)], which does not progress, especially if young, non-obese, and asymptomatic;
- associated conditions such as deafness, optic atrophy, or syndromic features; and
- a history of exposure to drugs known to be toxic to β cells or cause insulin resistance.

Characteristic features of youth onset type 1 diabetes in comparison with type 2 diabetes and monogenic diabetes are shown in Table 3. Type 2 diabetes is more completely discussed in the ISPAD guidelines on type 2 diabetes (3) and monogenic diabetes (18).

Regardless of the type of diabetes, however, the child who presents with severe hyperglycemia, ketonemia, and metabolic derangements will require insulin therapy initially to reverse the metabolic abnormalities.

Pathogenesis of type 1 diabetes

Type 1 diabetes is characterized by chronic immune-mediated destruction of pancreatic β -cells, leading to partial, or in most cases, absolute insulin deficiency. The majority of cases (type 1A) result from autoimmune mediated pancreatic β -cell destruction, which occurs at a variable rate, and becomes clinically symptomatic when approximately 90% of pancreatic

β -cells are destroyed. The etiology is multifactorial, however, the specific roles for genetic susceptibility, environmental factors, the immune system, and β -cells in the pathogenic processes underlying type 1 diabetes remain unclear.

Diabetes-associated autoantibodies, which are serological markers of β -cell autoimmunity, include GAD, IA2, IAA, and ZnT8 (16). The expression of these antibodies is age-dependent, with IAA and ZnT8 more commonly expressed in children aged <10 yr, while GAD and IA-2 are associated with older age and GAD with female gender (19).

Susceptibility to autoimmune type 1 diabetes is determined by multiple genes; with more than 60 risk loci identified by genome-wide association studies (20). Human leukocyte antigen (HLA) genotype confers approximately 50% of risk (21, 22); in the Caucasian population, specific combinations of HLA DR and DQ alleles determine genetic susceptibility (23). The highest-risk haplotypes are DRB1*03:01-DQA1*05:01-DQB1*02:01 and DRB1*04-DQA1*03:01-DQB1*03:02 (also expressed as DR3/DR4 or DQ2/DQ8 using the former serological designation). Haplotypes conferring protection from type 1 diabetes are DRB1*15:01-DQA1*01:02-DQB1*06:02, DRB1*14:01-DQA1*01:01-DQB1*05:03, and DRB1*07:01-DQA1*02:01-DQB1*03:03 (24). For individuals who are heterozygotes for the two highest risk HLA haplotypes (DR3/4), the odds ratio is 30 for development of islet autoimmunity and type 1 diabetes (24), however, <10% of those with HLA conferred diabetes susceptibility genes progress to clinical disease (25).

Individuals at increased risk of developing type 1 diabetes can be identified by a combination of diabetes-associated autoantibodies, genetic markers, intravenous glucose tolerance test (IVGTT) and/or OGTT (26–30).

The environmental triggers (infective and/or chemical) which initiate pancreatic β -cell destruction remain largely unknown, but the process usually begins months to years before the manifestation of clinical symptoms (28, 31, 32). Enterovirus infection has been associated with development of both islet autoimmunity and type 1 diabetes in many populations (33, 34) and enteroviruses have been detected in the islets of individuals with diabetes (35–37).

When the clinical presentation is typical of type 1 diabetes but antibodies are absent, then the diabetes is classified as type 1B (idiopathic). Most cases are of African or Asian ancestry, however, other forms of diabetes, including type 2 and monogenic diabetes, should also be considered (as shown in Table 2). In geographical areas where type 1 diabetes occurs with lower incidence, there is a higher rate of DKA at presentation (38).

Table 3. Clinical characteristics of type 1, type 2 and monogenic diabetes in children and adolescents

Characteristic	Type 1	Type 2	Monogenic
Genetics	Polygenic	Polygenic	Monogenic
Age of onset	6 months to young adulthood	Usually pubertal (or later)	Often postpubertal except GCK and NDM
Clinical presentation	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable (may be incidental in GCK)
Associations			
Autoimmunity	Yes	No	No
Ketosis	Common	Uncommon	Common in NDM, rare in other forms
Obesity	Population frequency	Increased frequency	Population frequency
Acanthosis nigricans	No	Yes	No
Frequency (% of all diabetes in young people)	Usually >90%	Most countries <10% (Japan 60–80%)	1–4%
Parent with diabetes	2–4%	80%	90%

Epidemiology of type 1 diabetes

In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, while across the lifespan, type 1 diabetes accounts for 5–10% of individuals with diabetes. Overall, approximately 80 000 children under 15 yr are estimated to develop type 1 diabetes annually worldwide (39). Type 2 diabetes is becoming more common and accounts for a significant proportion of youth onset diabetes in certain at-risk populations (3), but population-based epidemiological data are more limited compared with type 1 diabetes.

Older epidemiological incidence studies define the ‘onset of type 1 diabetes’ by the date of the first insulin injection because of the variable time between the onset of symptoms and diagnosis (40), while current guidelines define diabetes based on abnormal test results (as shown in Table 1).

Type 1 diabetes incidence varies greatly between different countries, within countries, and between different ethnic populations (Figure 1), with the highest incidence rates observed in Finland (41), Northern Europe (42–44), and Canada (45). There is an approximate 20-fold difference in the disease incidence among Caucasians living in Europe (25), and incidence rates are correlated with the frequency of HLA susceptibility genes in the general population (46, 47).

Of the estimated approximately 500 000 children living with type 1 diabetes, approximately 26% are from Europe, and 22% from North America and the Caribbean region (39). In Asia, the incidence of type 1 diabetes is very low, Japan approximately 2 per 100 000 person-years (48); China (Shanghai) 3.1 per 100 000 (49); Taiwan approximately 5 per 100 000 (50) and has a different and unique HLA association compared with Caucasians (51–54). In addition, there is a distinct slowly progressive form of type 1 diabetes in Japan,

which represents approximately one third of cases of type 1 diabetes (55, 56). Mean annual incidence rates for childhood type 1 diabetes (<age 15 yr) comparing different countries globally are shown in Fig. 1.

A seasonal variation in the presentation of new cases is well described, with the peak being in the winter months, whereas other reports demonstrate higher rates in warmer seasons (49) or variation from year to year (57–59). In addition, development of islet autoimmunity also demonstrates seasonal variation, as does the association between month of birth and risk of type 1 diabetes (60, 61).

In contrast to most autoimmune disorders, which disproportionately affect females, gender differences in the incidence of type 1 diabetes are found in some, but not all, populations. However, a male gender bias is generally observed in older adolescents and young adults (59, 62, 63).

A rise in type 1 diabetes incidence has been observed globally in recent decades (41, 43, 49, 50, 57–59, 64–72). In some reports there has been a disproportionately greater increase in those under the age of 5 yr (64, 73) and in developing countries or those undergoing economic transition in recent decades (64, 68). There is evidence for a plateau in incidence in some countries in recent years (41, 43, 69, 74, 75). The rising incidence of type 1 diabetes is associated with an increased proportion of individuals with low-risk HLA genotypes in some populations (76–78), suggesting an increasing role for environmental factors in the disease etiology.

Familial aggregation accounts for approximately 10% of cases of type 1 diabetes (79), but more than 20% when accounting for the extended family history (80), however, there is no recognizable pattern of inheritance. The risk of diabetes to an identical twin of a patient with type 1 diabetes is <40% (25, 81); for a sibling the risk is approximately 4% by age 20 yr (82, 83) and 9.6% by age 60 yr (49); compared with 0.5% for

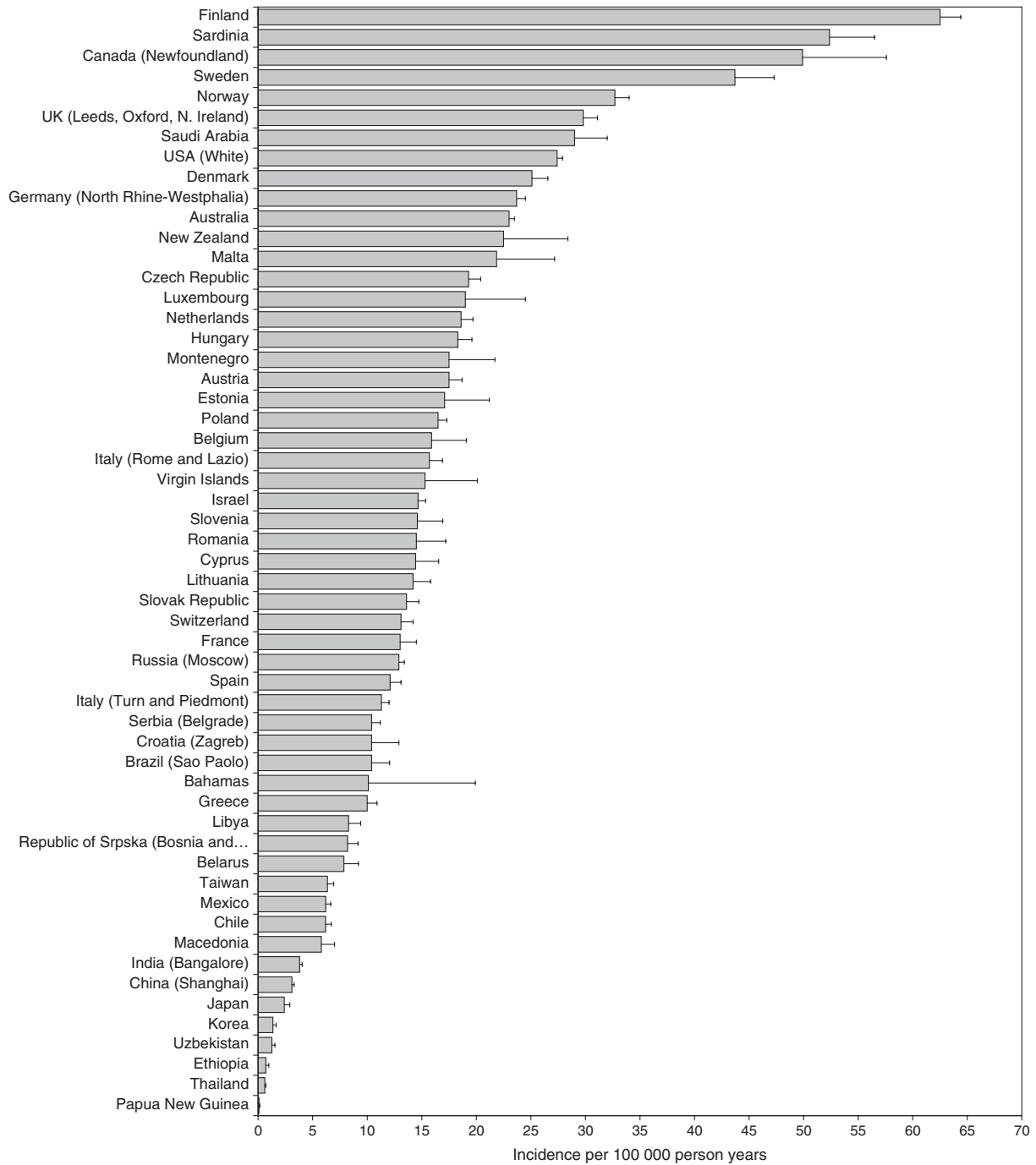


Fig. 1. Global mean annual incidence rates of type 1 diabetes in children and adolescents aged 0–14 yr. Only countries in which the study period included data from 2000 onwards are shown [adapted from the International Federation atlas (39)].

the general population. The cumulative risk of diabetes by age 15 is greater in HLA-identical DR3-DQ2/DR4-DQ8 siblings (17 vs. 6% in those sharing one haplotype or none) (84). The risk is also higher in siblings of probands diagnosed at younger age, paternal young-onset diabetes, male sex, and older parental age (82, 84, 85).

Type 1 diabetes is two to three times more common in the offspring of diabetic men (3.6–8.5%)

compared with diabetic women (1.3–3.6%) (85–90). The cumulative risk of type 1 diabetes is approximately 4% for offspring of adult onset (15–39 yr) type 1 diabetes (91), with a similar recurrence risk in the offspring of mothers and fathers.

Monogenic diabetes

A familial form of mild, non-ketotic diabetes present- ing during adolescence or early adulthood (92, 93),

originally termed maturity-onset diabetes of the young (MODY), is now recognized as a group of disorders which result from dominantly acting heterozygous mutations in genes important for the development or function of β cells (93, 94). Despite the classical description of MODY as a disorder with onset before 25 yr of age, autosomal dominant inheritance and non-ketotic diabetes mellitus (94, 95), it is clear that there is considerable overlap in the presentation of type 1, type 2, and monogenic diabetes. With the increased recognition of type 2 diabetes in young people, many will meet all of the 'classical' criteria for monogenic diabetes, but may initially be classified as having type 2 diabetes (96). Certain clinical characteristics should alert the clinician to the possibility of monogenic diabetes, as outlined in Table 3.

It is now considered more appropriate to define monogenic diabetes by its genetic subgroups, as shown in Table 2.

The most common form is associated with mutations in the transcription factor hepatocyte nuclear factor-1 α (*HNF1A*, also known as *MODY3*). Mutations in the glucokinase gene (*GCK*) and *HNF4A* contribute to the majority of remaining cases, while rare forms result from mutations in other transcription factors, including *HNF1B*, insulin promoter factor (*IPF*)-1, and *NeuroD1* (Table 2) (2, 94); for further detail see The ISPAD guideline on Monogenic Diabetes (18).

Within the diagnostic groups of monogenic diabetes, there is great variation in the degree of hyperglycemia, need for insulin, and risk for future complications.

Making a specific molecular diagnosis helps predict the expected clinical course of the disease, guide the most appropriate management for an individual, and has important implications for family members, enabling genetic counseling and extended genetic testing in other diabetic family members, whose diabetes may eventually be reclassified (97).

Neonatal diabetes

Type 1 diabetes rarely presents in the first year of life, particularly before age 6 months (98, 99), and in very young infants is most likely to be due to mutations in the transcription factor *FOXP3* as part of the immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) syndrome (100). A monogenic form of diabetes in the first 6 months of life is known as NDM, although cases may present as late 9–12 months of age (101–103). An alternative term, 'monogenic diabetes of infancy' has therefore been suggested to account for the fact that many cases are diagnosed beyond the neonatal period (104), but NDM is still widely used.

This rare condition (approximately 1 in 100 000–400 000 births) may be associated with

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intrauterine growth retardation, a consequence of prenatal insulin deficiency (105, 106), as well as a range of associated extra-pancreatic clinical features.

Approximately half of NDM cases will require lifelong treatment to control hyperglycemia (permanent NDM (PNDM)). In the remaining cases, diabetes remits within weeks or months (transient NDM (TNDM)), although may relapse later in life.

Approximately two thirds of cases of TNDM are caused by abnormalities in an imprinted region on chromosome 6q24 (107, 108). The majority of remaining cases result from activating mutations in either of the genes encoding the two subunits of the ATP-sensitive potassium (K_{ATP}) channel of the β -cell membrane (*KCNJ11*, encoding the Kir6.2 subunit, or *ABCC8*, encoding the SUR1 subunit) (109). Although diabetes is transient during infancy, permanent diabetes appears in 50–60% of patients later in life, typically around puberty (110).

PNDM is associated with activating mutations of *KCNJ11* and *ABCC8* (111, 112) and mutations in the insulin gene (*INS*) (113–117) and less commonly, *GCK* (118, 119) and the transcription factor for pancreatic development, *PDX1* (120). In addition, a range of syndromic forms of diabetes may present during infancy. Further details of the genetic basis of NDM are provided in the chapter on The diagnosis and management of monogenic diabetes in children and adolescents (18).

Mitochondrial diabetes

Mitochondrial diabetes is commonly associated with sensorineural deafness and is characterized by progressive non-autoimmune β -cell failure (121, 122). Maternal transmission of mutated mitochondrial DNA (mtDNA) can result in maternally inherited diabetes. The most common mutation occurs at position 3243 in the tRNA leucine gene, leading to an A-to-G transition (123, 124).

Mitochondrial diabetes may present with variable phenotypes, ranging from acute onset with or without ketoacidosis, to a more gradual onset resembling type 2 diabetes. The disease typically presents in young adults (121), but can occur in children and adolescents, who have a lower prevalence of hearing loss compared with adults (125).

Cystic fibrosis and diabetes

CFRD is the most common comorbidity associated with cystic fibrosis (CF). The pathophysiology of CFRD is primarily due to insulin deficiency, along with glucagon deficiency and variable insulin resistance (particularly during acute illness, secondary to infections and medications such as bronchodilators and glucocorticoids). Other contributory factors include the need for high caloric intake, delayed

gastric emptying, altered intestinal motility, and liver disease (126).

CF is associated with a progressive deterioration in glucose tolerance as individuals grow older, including indeterminate glycemia followed by IGT and finally diabetes. Early CFRD is characterized by normal fasting glucose levels, but over time fasting hyperglycemia develops.

CFRD typically presents in adolescence and early adulthood (127), but may occur at any age including infancy. The presentation may be asymptomatic, insidious, associated with poor weight gain (128), or precipitated by insulin resistance associated with infection/use of glucocorticoids. Detection rates for CFRD vary with screening practices (129). The onset of CFRD is defined as the date a person with CF first meets diabetes diagnostic criteria, even if hyperglycemia subsequently abates.

The onset of CFRD is a poor prognostic sign, and was associated with increased morbidity and mortality reported prior to implementation of routine screening for CFRD and early use of insulin therapy (130). Poorly controlled CFRD interferes with immune responses to infection and promotes protein catabolism (129, 131).

Annual screening for CFRD should commence by age 10 yr in all CF patients who do not have CFRD. Screening should be performed using the 2-h 75 g (1.75 g/kg) OGTT. A more comprehensive discussion can be found in the ISPAD guideline on CFRD (132).

Diabetes induced by drugs and toxins

A range of pharmacological agents impair insulin secretion (e.g., propranolol), and/or action (e.g., glucocorticoids, antipsychotic agents), while others (e.g., pentamidine) can cause permanent β -cell damage (2, 133, 134).

In neurosurgery, large doses of dexamethasone are frequently used to prevent cerebral edema. The additional stress of surgery may add to the drug-induced insulin resistance, and cause a relative insulin deficiency, sufficient to cause transient diabetes. Hyperglycemia may be exacerbated if large volumes of intravenous dextrose are given for management of diabetes insipidus. An intravenous insulin infusion is the optimal method to control the hyperglycemia, which is usually transient.

In oncology, protocols which employ L-asparaginase, high dose glucocorticoids, cyclosporin, or tacrolimus (FK506) may be associated with diabetes. L-Asparaginase usually causes a reversible form of diabetes (135). Tacrolimus and cyclosporin may cause a permanent form of diabetes possibly due to islet cell destruction (136). Often the diabetes is cyclical and associated with the chemotherapy

cycles, especially if associated with large doses of glucocorticoids.

Following organ transplantation, diabetes most frequently occurs with the use of high dose glucocorticoids and tacrolimus; the risk is increased in patients with preexisting obesity (137–139).

Diabetes can also be induced by the use of atypical antipsychotics including olanzapine, risperidol, quetiapine, and ziprasidone, which may be associated with weight gain. In children and adolescents, use of antipsychotics was associated with a more than threefold increased risk of non-autoimmune diabetes, and the risk was significantly higher with increasing cumulative dose (140). Among Canadian youth with medication-induced diabetes, risk factors for type 2 diabetes (family history of type 2 diabetes, obesity, non-caucasian ethnicity, and acanthosis nigricans) were less commonly observed than in youth with type 2 diabetes (141).

Stress hyperglycemia

Stress hyperglycemia has been reported in up to 5% of children presenting to an emergency department, in association with acute illness/sepsis; traumatic injuries, febrile seizures, burns, and elevated body temperature ($>39^{\circ}\text{C}$) (142–145). However, the incidence of severe hyperglycemia (≥ 16.7 mmol/L or 300 mg/dL) was $<1\%$ and almost two thirds of patients had received glucose-influencing interventions before evaluation, suggesting the etiology may at least in part be iatrogenic (146).

The reported incidence of progression to overt diabetes varies from 0 to 32% (145, 147–152). Children with incidental hyperglycemia without a serious concomitant illness were more likely to develop diabetes than those with a serious illness (150). As would be expected, testing for diabetes-associated autoantibodies had a high positive and negative predictive value for the development of type 1 diabetes in children with stress hyperglycemia (150). In children who have sustained severe burns, insulin resistance may persist for up to 3 yr later (144).

Conflicts of interest

The authors have declared no conflicts of interest.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Phases of type 1 diabetes in children and adolescents

Couper JJ, Haller MJ, Ziegler A-G, Knip M, Ludvigsson J, Craig ME. Phases of type 1 diabetes in children and adolescents.

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- No interventions at present are proven to prevent or delay the onset of type 1 diabetes (A).
- Neither screening of any population nor intervention in the preclinical phase (primary and secondary prevention) or after diagnosis (tertiary prevention) should be performed outside the context of defined research studies (E).
- Individuals who screen positive for genetic or immunological markers of type 1 diabetes should have access to appropriate counseling and information regarding research studies (E).
- In children whose diabetes is diagnosed in the pre-clinical phase (e.g., stage 3), commencement of insulin therapy should be considered when hemoglobin A1c (HbA1c) > 6.5% (E).
- All primary, secondary, and tertiary prevention studies should be registered as clinical trials, and

information about ongoing studies should be readily available (E).

- Parents and children with type 1 diabetes should be counseled that the remission phase of diabetes is transient and does not indicate total remission of diabetes. At present no single agent is known to restore β -cell function for an extended period of time (A).

Type 1 diabetes is characterized by stages, ranging from asymptomatic preclinical diabetes to chronic established diabetes with long-term complications. The proposed stages are:

Stage description

- (i) Autoimmunity, no dysglycemia, asymptomatic
- (ii) Autoimmunity and dysglycemia [impaired oral glucose tolerance test (OGTT) and/or impaired fasting glucose (IFG)], asymptomatic

- (iii) Autoimmunity, diabetic OGTT, diabetic FG, asymptomatic
- (iv) New onset symptomatic type 1 diabetes
- (v) Established type 1 diabetes
- (vi) Established type 1 diabetes with long-term complications

Genetic susceptibility

More than 60 genetic variants have been identified in association with type 1 diabetes by genome-wide association studies (1). The human leukocyte antigen (HLA) genotype confers approximately half of the genetic risk for type 1 diabetes (2, 3). In the Caucasian population, specific combinations of DR and DQ alleles at the HLA loci determine genetic susceptibility, conferring increased or decreased risk (4). The highest risk haplotypes are DRB1*03:01-DQA1*05:01-DQB1*02:01 and DRB1*04-DQA1*03:01-DQB1*03:02 (also expressed as DR3/DR4 or DQ2/DQ8 using the former serological designation). Haplotypes conferring protection from type 1 diabetes are DRB1*15:01-DQA1*01:02-DQB1*06:02, DRB1*14:01-DQA1*01:01-DQB1*05:03 and DRB1*07:01-DQA1*02:01-DQB1*03:03 (5). Genotyping at birth can stratify diabetes risk and identify a population with a 10-fold increased risk of type 1 diabetes.

Pre-clinical diabetes

Preclinical diabetes (stages 1–3) refers to the months or years preceding the clinical presentation of type 1 diabetes when islet antibodies can be detected as markers of β -cell autoimmunity (6):

- Glutamic acid decarboxylase 65 autoantibodies (GAD)
- Tyrosine phosphatase-like insulinoma antigen 2 (IA2) and islet cell antibody 512 (ICA512)
- Insulin autoantibodies (IAA)
- β -cell-specific zinc transporter 8 autoantibodies (ZnT8)

Risk of progression to diabetes

For individuals who are heterozygotes for the two highest risk HLA haplotypes (DR3/4), the odds ratio is 30 for development of islet autoimmunity and type 1 diabetes (5). First-degree relatives (FDR) with DR3/DR4 (or DQ2/DQ8) have a greater risk of type 1 diabetes compared with individuals in the general population possessing these genotypes, consistent with the contribution of other risk loci (7). Predictive algorithms that also incorporate non-HLA genetic markers, such as the protein tyrosine phosphatase

non-receptor (PTPN22) gene or the insulin gene (INS), further improve risk estimates for type 1 diabetes, particularly for individuals with DR3/DR4 in the general population (8).

The majority of children at risk of type 1 diabetes with multiple islet antibody seroconversion progress to diabetes within the next 15 yr. Approximately 70% with seroconversion of multiple islet autoantibodies progress to diabetes over 10 yr, compared to 15% with a single islet antibody. Progression in children with multiple islet antibodies is faster when seroconversion is before 3 yr, and in children with the HLA DR3/DR4-DQ8 genotype (9). Among islet autoantibody-positive children, a combination of five genes (INS, IFIH1, IL18RAP, CD25, and IL2) identified 80% of children who progressed to diabetes within 6 yr of seroconversion (10). A risk score could further separate those at high vs. low risk of progression.

In addition to immune and genetic markers, the risk of type 1 diabetes may be refined further by measurement of insulin release in response to an intravenous glucose load (IVGTT). Impaired first phase insulin release on IVGTT (defined as an insulin response less than the 10th percentile for age and sex-matched controls) confers a 60% risk of developing type 1 diabetes over the next 5 yr (11). However, it has been suggested that the IVGTT may not be required as a prognostic tool; in antibody positive FDRs with normal glucose tolerance in the DPT-1 trial, the 2-h glucose level on OGTT demonstrated the greatest accuracy for predicting progression to type 1 diabetes (12). Furthermore, in those with abnormal glucose tolerance, the combination of 2-h glucose, peak C-peptide, and area under the curve C-peptide significantly improved the prognostic accuracy compared with a single measure (13).

The global increase in the incidence of type 1 diabetes over the last 30 yr, in parallel with a reduction in the proportion of individuals with high-risk HLA haplotypes in some populations (14–16) confirms the role of the environment in its pathogenesis; this is likely through complex gene–environment interactions and epigenetic mechanisms. There is also heightened interest in the interaction of the environment with biological systems (including the microbiome, metabolome, and lipidome), which in turn can regulate immune tolerance. Congenital rubella is a long standing recognized environmental trigger (17, 18). Other putative exposures are enterovirus infections (19), and the introduction of foreign antigens in the infant diet, including casein, bovine insulin (20), root vegetables, and cereals (21, 22). Exclusive breast feeding for >2 wk may have a modest protective effect; odds ratio: 0.75 (95% CI: 0.64–0.88) (23). In at-risk children, concurrent breast milk feeding at the time of cereal introduction may be protective (21). Omega-3

fatty acids may also have a small protective effect (24). Vitamin D metabolism may play, as yet, an undetermined role (25–27). The modern environment provides for excess nutrition, rapid growth, and weight gain in early life and an accompanying reduction in insulin sensitivity. This may accelerate both development of islet autoimmunity and progression to type 1 diabetes (28, 29). International networks following children at increased genetic risk from pregnancy or birth are investigating these questions (9, 30, 31).

Prevention of diabetes

Primary prevention

Primary prevention trials begin prior to development of islet autoimmunity, typically in infants at increased genetic risk of type 1 diabetes. As the majority of participants would not be expected to progress to clinical disease, the intervention must be benign.

- The BABY DIET study showed no benefit from delaying gluten exposure until 12 months of age in at-risk children (32).
- The FINDIA study showed that weaning to a cow's milk formula free of bovine insulin reduced the cumulative incidence of islet autoantibodies by age 3 in children at genetic risk of type 1 diabetes mellitus, with an odds ratio of 0.23 (95% CI: 0.08–0.69) (33).
- The TRIGR pilot trial, conducted in Finland, showed that intervention with a casein hydrolysate formula from the time of weaning formula during infancy halved the risk of development of one or more islet autoantibodies (hazard ratio: 0.51, 95% CI: 0.28–0.91) (34). The international TRIGR trial is exploring this intervention in 2159 infants with high-risk HLA genotypes from across Europe, North America, and Australia (35). The recent analysis of the first endpoint, i.e., positivity for at least two islet autoantibodies by the age of 6, showed no difference in the appearance of autoantibodies between those participants randomized to weaning to an extensively hydrolyzed formula and those randomized to be weaned to a conventional formula (36). The trial will, however, continue to assess the final endpoint, which is clinical diabetes by the age of 10.
- Other primary prevention trials currently underway include the Nutritional Intervention to Prevent (NIP) type 1 Diabetes pilot study to determine the effect of omega-3 fatty acid supplementation from late gestation on risk of islet autoimmunity (37), and primary intervention with oral insulin for prevention of type 1 diabetes in infants at high genetic risk to develop diabetes (Pre-Point) (38).

Secondary prevention

Secondary prevention trials intervene after development of islet autoimmunity, prior to the onset of clinical disease.

- The European Nicotinamide Diabetes Intervention Trial (ENDIT), demonstrated that nicotinamide did not delay or prevent the onset of type 1 diabetes in high-risk FDRs (39).
- The National Institute of Health Diabetes Prevention Trials (DPT) demonstrated that neither low dose subcutaneous nor oral insulin therapy delayed or prevented the onset of clinical diabetes in high-risk and intermediate-risk FDRs, respectively (11, 40). However, in a post-hoc analysis of those subjects with high insulin autoantibody titers, therapy with oral insulin delayed progression to type 1 diabetes (by 4.5 yr) (40). This observation is now being prospectively retested in the TrialNet Oral Insulin study (41).
- Secondary prevention trials currently in progress include anti-CD3 monoclonal antibody (Teplizumab); CTLA-4 Ig (Abatacept), which modulates co-stimulation and prevents full T-cell activation, for prevention of diabetes in relatives at risk for type 1 diabetes (both conducted by TrialNet); the Australasian intranasal insulin trial II (INIT II) (42, 43) and the CoRD pilot trial (44).

At the present time, there are no interventions proven to prevent or delay the clinical manifestation of type 1 diabetes. Therefore, neither screening of any population nor intervention in the preclinical phase should occur outside the context of defined research studies (7). Individuals who screen positive for genetic or immunological markers of type 1 diabetes should have access to counseling and appropriate information about research studies.

Presentation of type 1 diabetes

Prospective follow-up of high-risk individuals shows that diagnosis of type 1 diabetes can be made before symptoms develop (i.e., stage 3) in the majority of cases (11) and that their risk of diabetic ketoacidosis is reduced (45).

A child presenting with a classical history of increasing polyuria, polydipsia, and weight loss over 2–6 wk (stage 4) presents a straightforward diagnosis. However, failure to consider the possibility of diabetes or atypical presentations may result in late diagnosis and an increased risk of diabetic ketoacidosis (46). Some children have a rapid onset of symptoms and present within days in diabetic ketoacidosis; others have a slow onset of symptoms over several months. Clinical presentation of diabetes can range from

non-emergency presentations to severe dehydration, shock, and diabetic ketoacidosis (Table 1).

Urinary 'dipstick' testing for glucosuria and ketonuria, or measurement of glucose and ketones using a bedside glucometer, provides a simple and sensitive tool for excluding diabetes with less typical presentation. A blood glucose measurement (plasma glucose > 11.1 mmol/L) confirms the diagnosis; this should be based on a laboratory glucose oxidase estimation rather than a capillary blood glucose monitor.

If a child has symptoms of diabetes, immediate referral to a center with expertise in the care of such children is mandatory, as prompt diagnosis and treatment of diabetes in children is important in preventing rapid deterioration into ketoacidosis. Severe ketoacidosis if untreated is fatal. Therapy is urgent and referral to specialized services is essential. See Chapter 10 – Diabetic Ketoacidosis (47). In children whose diabetes is diagnosed in the pre-clinical phase (e.g., stage 3), commencement of insulin therapy should be considered when HbA1c > 6.5%.

Differentiating between type 1 and type 2 diabetes at diagnosis

Features suggesting the diagnosis of type 2 diabetes rather than type 1 diabetes at diagnosis include (see also Chapter 3 – Type 2 diabetes (48)):

- Overweight or obesity
- Age above 10
- Strong family history of type 2 diabetes
- Acanthosis nigricans
- High-risk racial or ethnic group
- Undetectable islet autoantibodies
- Elevated C-peptide (since there is considerable overlap in insulin or C-peptide measurements between type 1 and type 2 diabetes in the first year after diagnosis, C-peptide measurements are not recommended in the acute phase)

The overweight epidemic in many countries has resulted in up to one third of children presenting with overweight or obesity at diagnosis of type 1 diabetes (49, 50), with accompanying insulin resistance. Detectable islet autoantibodies confirm the diagnosis of type 1 diabetes and the need for insulin therapy.

Partial remission or honeymoon phase in type 1 diabetes

In approximately 80% of children and adolescents, insulin requirements decrease transiently following initiation of insulin treatment (51); this is thought to reflect partial β -cell recovery with increased insulin

secretion and improved peripheral insulin sensitivity (52).

The partial remission phase may be defined as an insulin requirement of <0.5 units/kg of body weight per day and HbA1c < 7% (51). Recently, insulin dose adjusted HbA1c, defined as HbA1c (%) + 4 \times [insulin dose in units/kg/24 h] has been proposed as a more specific measure of remission (53, 54).

The phase commences within days or weeks of the start of insulin therapy and may last for weeks to years. During this period, blood glucose levels are frequently stable within the normal range, despite fluctuations in diet and exercise. Ketoacidosis at presentation (55), and younger age at diabetes onset reduce the likelihood of a remission phase (53, 56).

Intensive therapy leads to better metabolic control and a reduction in insulin requirements (57). While there may be a transient effect of intensive therapy on β -cell function, the effect is not sustained (58). Nevertheless, preserving β -cell function decreases the risk of developing vascular complications and severe hypoglycemia (57, 59). Most people with recent onset type 1 diabetes retain some β -cell function that may persist for decades following diagnosis (60, 61).

There is an international network of intervention trials to preserve β -cell function from diagnosis (62). Immune modulation therapies include Teplizumab (63), Abatacept (64, 65), and the anti-CD20 monoclonal antibody, rituximab; all of which can delay for some time the loss of β -cell function after the diagnosis in patients with recent onset diabetes (66), including children and adolescents (67). Combination immune therapy via autologous non-myeloablative hematopoietic stem cell transplant has had the most success in restoring β -cell function in the short term (68). However, as there are considerable risks involved, additional efforts are underway to develop effective combination therapies with more acceptable risk profiles (e.g., anti-thymocyte globulin and granulocyte colony stimulation factor). Antigen-based therapies have shown less success, apart from variable increase in C-peptide in adults receiving DiaPep277, a peptide derived from heat shock protein 60 (69–72) and with GAD alum treatment (71, 72). Cell therapies including autologous expanded regulatory T cells and umbilical cord blood infusion (73) are well tolerated and under investigation but have yet to demonstrate the capacity to preserve β -cell function. Anti-inflammatory agents and GLP-1 agonists, that stimulate β -cell repair and regeneration, are also potential agents, as well as combination therapy with Vitamin D and Etanercept. Ultimately a targeted combination approach is likely to be the most effective (74, 75).

Parents and children with type 1 diabetes should be counseled that the remission phase of diabetes is transient and does not indicate total remission of

Table 1. Clinical characteristics at presentation of type 1 diabetes

Non-emergency presentations

- Recent onset of enuresis in a previously toilet-trained child, which may be misdiagnosed as a urinary tract infection
- Vaginal candidiasis, especially in pre-pubertal girls
- Chronic weight loss or failure to gain weight in a growing child
- Irritability and decreasing school performance
- Recurrent skin infections

Emergency presentations (Diabetic ketoacidosis or hyperosmolar hyperglycemia) (47)

- Moderate to severe dehydration
- Frequent vomiting and in some cases, abdominal pain, which may be misdiagnosed as gastroenteritis
- Continuing polyuria despite the presence of dehydration
- Weight loss due to fluid loss and loss of muscle and fat
- Flushed cheeks due to ketoacidosis
- Acetone detected on the breath
- Hyperventilation of diabetic ketoacidosis (Kussmaul respiration), characterized by an increased respiratory rate and large tidal volume of each breath, which gives it a sighing quality
- Disordered sensorium (disoriented, semi-comatose, or rarely comatose)
- Shock (rapid pulse rate, poor peripheral circulation with peripheral cyanosis)
- Hypotension (a very late sign and rare in children with diabetic ketoacidosis)

Diagnostic difficulties that may lead to late diagnosis

- Very young children may present in severe ketoacidosis because of a more rapid onset of severe insulin deficiency (19) and because the diagnosis was not considered earlier
- The hyperventilation of ketoacidosis may be misdiagnosed as pneumonia or asthma (cough and breathlessness distinguish these conditions from diabetic ketoacidosis)
- Abdominal pain associated with ketoacidosis may simulate an acute abdomen and lead to referral to a surgeon
- Polyuria and enuresis may be misdiagnosed as a urinary tract infection
- Polydipsia may be thought to be psychogenic
- Vomiting may be misdiagnosed as gastroenteritis or sepsis

diabetes. At present, no single agent is known to restore β -cell function for an extended period of time.

Chronic phase of lifelong dependence on insulin

The progression from the partial remission phase into the chronic phase of dependence on exogenous insulin is usually a gradual decrease in residual β -cell function. However, ultra-sensitive C-peptide assays show that some long-term endogenous insulin production persists in up to 75% of patients (61). At present, exogenous insulin is the only form of replacement therapy for children and adolescents with type 1 diabetes.

β -cell replacement therapies

Islet transplantation has become more successful as the introduction of less β -cell toxic immunosuppressive agents and refined techniques to harvest adequate numbers of viable β -cell (76, 77). At present, its main indication is to treat hypoglycemic unawareness that is not responsive to other measures, such as continuous subcutaneous insulin infusion, in adults with type 1 diabetes. Less than half (44%) of recipients remain insulin independent at 3 yr post-transplant

and approximately 25% at 5 yr (78). The shortage of human cadaveric donor pancreata, particularly given that approximately half of transplant recipients require a second infusion, and the current need for lifelong immunosuppression limit the use of islet transplantation. Therefore, the development of encapsulated β -cell that is protected from immune attack is a major goal. Advances in β -cell and stem cell biology provide promise of developing human pancreatic endocrine cell progenitors from human embryonic stem cells as a replacement therapy (79, 80).

Conflict of interest

The authors have declared no conflict of interest.

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Phases of type 1 diabetes in children and adolescents

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Type 2 diabetes in the child and adolescent

Zeitler P, Fu J, Tandon N, Nadeau K, Urakami T, Bartlett T, Maahs D. Type 2 diabetes in the child and adolescent.

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

Screening for T2D in at-risk youth

- Undiagnosed type 2 diabetes (T2D) is very rare in the adolescent population (A).
- Generalized screening of obese youth is unlikely to be cost-effective in most populations (E).
 - Urinary glucose screening in Japanese adolescents may be a specific case with demonstrated cost effectiveness.
- Clinical testing for dysglycemia in obese at-risk youth should occur in the setting of clinical assessment of obesity-related comorbidities [non-alcoholic fatty liver disease (NAFLD), elevated triglycerides, elevated blood pressure (BP)] that are more prevalent than dysglycemia (E)

Diagnosis and determination of diabetes type

- T2D in youth should be diagnosed using American Diabetes Association (ADA) criteria (E)

- Diagnosis can be made based on fasting glucose, 2-h postchallenge glucose, or hemoglobin A1c (HbA1c).
- In the absence of symptoms, testing should be confirmed on a different day.
- Clinicians should be aware of the weaknesses of each diagnostic test.
- Diabetes autoantibody testing should be considered in all pediatric patients with the clinical diagnosis of T2D because of the high frequency of islet cell autoimmunity in otherwise 'typical' T2D (E).
 - Prepubertal children are unlikely to have T2D even if obese (A).
 - Antibodies will indicate the diagnosis of type 1 diabetes (T1D) and an earlier need for insulin (A).
 - Antibodies will indicate the need to consider the presence of other associated autoimmune disorders (A).

- Diabetes autoantibody testing should be considered in overweight/obese pubertal children with a clinical picture of T1D (A).

- The presence of clinically relevant associated complications and comorbidities should be assessed at the time of diagnosis (A).
 - Triglycerides and liver enzymes should be obtained at the time of diagnosis to exclude acute clinically relevant abnormalities (E).
 - Urine albumin/creatinine ratio (ACR) should be obtained at the time of diagnosis.
 - Patients should be screened for obstructive sleep apnea (OSA), pregnancy, and depression at the time of diagnosis (E).

Initial treatment

- Lifestyle change should be initiated at the time of diagnosis of T2D (E).
- Initial pharmacologic treatment of youth with T2D should include metformin and insulin alone or in combination (A).
- Initial treatment is determined by symptoms, severity of hyperglycemia, and presence or absence of ketosis/ketoacidosis (E).
 - Patients with symptoms can deteriorate rapidly irrespective of eventual diabetes type and need urgent assessment and appropriate treatment (E).
 - Metabolically stable patients (HbA1c < 9 and no symptoms) should be started on metformin monotherapy (A).
 - (i) Begin with 500 mg daily × 7 d. Titrate by 500 mg once a week over 3–4 wk to the maximal dose of 1000 mg twice-daily (BID) (extended release metformin product may be used where available).
 - Patients who are not metabolically stable require insulin (A).
 - (i) Once a day NPH or basal insulin (0.25–0.5 units/kg starting dose) is often effective in attaining metabolic control.
 - (ii) Metformin can be started at the same time as insulin, unless acidosis is present.
 - (iii) Transition onto metformin monotherapy can usually be achieved safely over 2–6 wk.
- The goal of initial treatment should be HbA1c < 6.5% (B).
- Self-monitored blood glucose (SMBG) should be performed regularly. The frequency of SMBG should be individualized based on the degree of glycemic control and available resources (E).

Subsequent treatment

- If the patient fails to reach target HbA1c of < 6.5% within 3–4 months on metformin monotherapy, addition of basal insulin should be strongly considered (A).
- If target is not attained on combination metformin and basal insulin (up to 1.2 U/kg), prandial insulin should be initiated and titrated to reach target HbA1c < 6.5% (B).
- There are limited studies of the use of other pharmacologic agents and they are generally not approved in this population (E).

Assessment and management of comorbidities and complications

- Urine ACR should be obtained at the time of diagnosis and annually thereafter (A):
 - (i) An elevated urine ACR should be confirmed on 2 of 3 samples.
 - If elevated urine ACR is confirmed, angiotensin-converting enzyme (ACE) inhibitor should be started and titrated every 3 months until ratio is normal (A).
- BP should be monitored at every visit according to standardized techniques specific for children (A).
 - (i) Elevated BP should be confirmed on 2 additional days.
 - (ii) Hypertension is defined as an average systolic or diastolic BP > 95 percentile for age, sex, and height percentiles, with high normal BP being 90 to < 95 percentile.
 - Initial treatment should consist of weight loss, limitation of dietary salt, and increased physical activity (E).
 - If BP is above the 95th percentile after 6 months, an ACE inhibitor is initiated and titrated to achieve BP less than the 90th percentile (A).
- Testing for dyslipidemia should be repeated soon after diagnosis when glycemic control has been achieved and annually thereafter (A).
 - (i) If the ACE inhibitor is not tolerated due to adverse effects, an angiotensin receptor blocker, calcium channel blocker, or diuretic can be used (E).
 - (ii) Combination therapy may be required if hypertension does not normalize on single agent therapy (E).

- Cholesterol
 - (i) Goal levels are:
 - Low-density lipoprotein cholesterol (LDL-C) <100 mg/dL (2.6 mmol/L)
 - High-density lipoprotein cholesterol (HDL-C) >35 mg/dL (0.91 mmol/L)
 - Triglycerides <150 mg/dL (1.7 mmol/L)
 - (ii) If LDL-C is above goal, blood glucose control should be maximized and dietary counseling should be provided using the American Heart Association (AHA) step 2 diet.
 - A repeat fasting lipid profile should be performed in 6 months.
 - (iii) If repeat LDL-C >130 mg/dL: begin medication with a goal of <130 mg/dL an ideal target of <100 mg/dL (E).
 - (iv) Statin therapy has been shown to be safe and effective (A).
- Triglycerides
 - (i) If triglycerides are >400 mg/dL fasting or >1000 mg/dL non-fasting: begin medication with a goal of <400 mg/dL fasting (to reduce risk for pancreatitis) (E).
 - (ii) Fibrate therapy is the preferred medication category for hypertriglyceridemia and has been shown to be safe and effective (A).
- Examination for retinopathy should be performed at diagnosis and annually thereafter (A).
- Evaluation for NAFLD should be done at diagnosis and annually thereafter (A).
 - Patients should be referred to gastroenterology if liver enzymes remain elevated despite weight loss and attainment of glycemic control (E).
- Patients should be screened for menstrual irregularities, hyperandrogenism, depression, and OSA at diagnosis and regularly thereafter (E).
- Patients should be screened for smoking and alcohol use at diagnosis and regularly thereafter (E).

Introduction

T2D in children and adolescents (youth-onset T2D) has become an increasingly important public health concern throughout the world (1–17), with unique characteristics and demographics in many countries.

Because of the relatively recent emergence of the problem in this age group, there has been a limited evidence base leading to unique challenges in the diagnosis, management, and monitoring of these individuals. This limited evidence base is further complicated by differences in the characteristics and presentation of the disorder and approaches to treatment in developed and developing countries. In 2009, ISPAD developed guidelines for the diagnosis and management of children and adolescents with T2D (18). Since the publication of those guidelines, a number of important studies have been designed and completed that contribute substantially to understanding of T2D. This chapter will discuss the diagnosis and presentation of T2D, classification of diabetes type, initial and subsequent treatment, monitoring and assessment, and management of associated comorbidities and complications.

Definition, classification, and characteristics of youth-onset T2D

T2D occurs when insulin secretion is inadequate to meet the increased demand posed by insulin resistance, leading to relative insulin deficiency (19) and is generally associated with other metabolic abnormalities, characteristic of insulin resistance (dyslipidemia, hypertension, polycystic ovary syndrome, fatty liver) (20). Unlike T1D, there is no identified autoimmune process leading to inadequate insulin secretion in T2D (20) and inadequate insulin secretion appears to result from genetic, environmental, and metabolic causes may differ between individuals. Insulin secretion depends on disease status and duration, and can vary from delayed but markedly elevated in response to a glucose challenge initially to absolutely diminished (19). Adults with symptoms of diabetes have 50% reduction in insulin secretion at the time of diagnosis and may become insulin-dependent within a few years (21). Recent data from the TODAY (Treatment Options for T2DM in Adolescents and Youth) study suggest that the loss of insulin secretion is even more rapid when T2D presents in adolescents (22, 23).

The diagnosis of T2D requires two steps: confirmation of the presence of diabetes followed by determination of diabetes type. The criteria and classification of diabetes are presented in greater detail in the ISPAD Clinical Practice Consensus Guidelines: Definition, Epidemiology, Diagnosis and Classification of Diabetes (24). The diagnostic criteria for diabetes are based on the measurement of glycemia and the presence of symptoms (25). There are four accepted ways to diagnose diabetes and each, in the absence of unequivocal symptoms of hyperglycemia,

must be confirmed, on a subsequent day, by any one of the four methods given below.

Diabetes is diagnosed when:

- Fasting plasma glucose (FPG) is ≥ 7.0 mmol/L (126 mg/dL).
- Postchallenge plasma glucose is ≥ 11.1 mmol/L (200 mg/dL).
 - 1.75 g/kg (max 75 g) anhydrous glucose dissolved in water.
- Symptoms of diabetes and a casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L).
 - Casual is defined as any time of day without regard to time since last meal.
 - Symptoms of diabetes include polyuria, polydipsia, nocturia, and unexplained weight loss.
- HbA1c $> 6.5\%$.
 - Must utilize a laboratory based, DCCT aligned, National Glycohemoglobin Standardization Program certified methodology.
- In the absence of symptoms, hyperglycemia detected incidentally or under conditions of acute physiologic stress may be transitory and should not be regarded as diagnostic of diabetes.
- Studies have raised concerns about the reproducibility of the oral glucose tolerance test (OGTT) in obese adolescents, with a concordance rate between repeat OGTTs a few weeks apart of approximately 30% (26).
- Although the HbA1c criterion has been accepted by the ADA for the diagnosis of diabetes in adults, this criterion remains controversial, as it identifies a population that does not overlap entirely with that identified by fasting or postglucose challenge criteria (27). However, HbA1c $> 6.5\%$ predicts the risk of retinopathy as well as the glucose criteria. The application of HbA1c criteria for children has not been established and caution should be used when relying solely on HbA1c for diagnosis.

After the diagnosis of diabetes is established, diabetes autoantibody testing should be considered in all pediatric patients with the clinical diagnosis of T2D because of the high frequency of islet cell autoimmunity in patients with otherwise 'typical' clinically defined T2D. Studies have shown that autoantibodies are present in 10–20% of patients clinically diagnosed with T2D, depending on the race and ethnicity of the population (21, 28–32). The presence of antibodies predicts rapid development of insulin requirement

(33), as well as risk for development of other autoimmune disorders. Diabetes autoantibody testing should also be considered in overweight/obese pubertal children with a clinical picture of T1D (weight loss, ketosis/ketoacidosis), some of whom may have T2D and be able to wean insulin off for extended periods of time with good control (34).

Characteristics of individuals with youth-onset T2D

- Youth-onset T2D occurs most often during the second decade of life, with a median age of diagnosis of 13.5 yr. This coincides with the peak of physiologic pubertal insulin resistance, which may lead to onset of overt diabetes in previously compensated adolescents. Accordingly, the median age of onset is 1 yr later in boys than girls (8, 35).
- Youth-onset T2D rarely occurs prior to puberty (8, 35).
- Youth with T2D come from families with a high prevalence of T2D in first and second degree relatives (35, 36).
- Youth-onset T2D occurs in all races, but at a much greater prevalence in those of non-White European descent, e.g., those of Black African descent, native North American, Hispanic (especially Mexican)-American, Asian, South Asian (Indian Peninsula), and Native Pacific islanders. The SEARCH for Diabetes in Youth population-based study found the proportion of physician diagnosed T2D among 10–19 yr olds to vary greatly by ethnicity in the USA: 6% for non-Hispanic Whites, 22% for Hispanics, 33% for Blacks, 40% for Asians/Pacific Islanders, and 76% for Native Americans (8).
- In Hong Kong, 90% of youth-onset diabetes is T2D (10), in Taiwan 50% (11) and nearly 60% in Japan.
- In the USA and Europe, nearly all youth with T2D have body mass index (BMI) above 85th percentile for age and sex (35). However, this is not true in Asia. In Japan, 15% of children with T2D are not obese (17, 37). In Asian Indian urban children, half of those with T2D had normal weight ($< 120\%$ ideal for height) (12), and half of Taiwanese children with T2D were not obese (11).
- Youth-onset T2D has a sex ratio (male:female) that varies from 1:4–1:6 in native North Americans to 1:1 in Asians and Libyan Arabs.
- In the USA and Europe, youth-onset T2D is predominately found in populations characterized by low socioeconomic and educational status (35), whereas in emerging countries like China and India, more affluent children are more likely to develop T2D than poorer children.
- The presentation of youth-onset T2D can vary from asymptomatic hyperglycemia detected through screening or during routine physical examination

to ketoacidosis in up to 25% of patients (38) or hyperglycemic hyperosmolar state (39). These latter two presentations can entail significant risk for morbidity and mortality if not recognized and treated.

Autoimmune 'T2D'

Some authors have reported the phenomenon of autoimmune T2D. This has sometimes been referred to as T1.5, T3, or double diabetes. However, it is now becoming clearer that these individuals are best understood as having autoimmune T1D presenting in overweight or obese individuals with underlying insulin resistance.

- Youth and adults in USA and Europe who are clinically diagnosed with T2D are found to have T1D-associated autoantibodies in 15–40% of cases, including many who are not receiving insulin 1 yr after diagnosis (28–31).
- Antibody positive youth with the T2D phenotype are significantly less overweight, have lower BP, lower triglycerides, higher HDL-C, are less likely to be female and more likely to be non-minority than otherwise similar antibody negative patients (21, 28, 32).
- β -cell function is significantly less in antibody positive youth with T2D phenotype, resulting in more rapid development of insulin dependence (28, 31, 32).

Uncertainties of classification

The clinician is obliged to weigh the evidence in each individual patient to distinguish between T1D and T2D. The reasons for this conundrum are:

- With increasing obesity in childhood, as many as 30% of newly diagnosed T1D (or monogenic diabetes) patients may be obese, depending on the rate of obesity in the background population.
- A significant number of pediatric patients with T2D demonstrate ketonuria or ketoacidosis at diagnosis (2).
- T2D is common in the general adult population with a positive family history for diabetes in 15% or greater in minority populations, reducing the specificity of a positive family history.
- There is considerable overlap in insulin or C-peptide measurements between T1D and T2D at onset of diabetes and over the first year or so (8). This overlap is due to the recovery phase of autoimmune-mediated T1D (the honeymoon) and the effects of elevated glucose (glucotoxicity) and free fatty acids (FFAs) (lipotoxicity) to impair insulin secretion at

the time of testing in both T1D and T2D. In addition the insulin resistance of obesity raises residual C-peptide levels in obese adolescents with T1D. Such measurements are thus relatively valueless in the acute phase. However, persistence of c-peptide above the normal level for age would be unusual in T1D after 12–14 months (36).

- Insulin resistance is present in both T2D and T1D, though the pathophysiology is different and resistance in T2D is generally more severe (40, 41).
- Measurement of diabetes autoantibodies is the most rigorous approach to identification of T1D. However, this measurement may be limited by lack of ready availability of standardized autoantibody assays, cost, involvement of antibodies not yet identified, and varying rates of antibody positivity in T1D in different ethnic groups

Prediabetes: diagnostic criteria (impaired glucose tolerance and impaired fasting glycemia)

There are individuals whose glucose levels do not meet the criteria for diabetes, but are too high to be considered normal. The ADA had designated this physiologic state prediabetes to recognize the high risk of progression of these individuals to diabetes (25).

- Impaired glucose tolerance (IGT) and impaired fasting glycemia (IFG) are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes.
- IFG and IGT are not interchangeable and represent different abnormalities of glucose regulation. IFG is a measure of disturbed carbohydrate metabolism in the basal state, whereas IGT is a dynamic measure of carbohydrate intolerance after a standardized glucose load (42).
- Individuals who meet the criteria for IGT or IFG may be euglycemic in their daily lives, as shown by normal or near-normal glycosylated hemoglobin levels, and those with IGT may manifest hyperglycemia only when challenged with an OGTT.
- Some individuals may have elevated glycosylated hemoglobin levels but have normal OGTT, likely reflecting daily carbohydrate intake exceeding that associated with a standard glucose load.
- In obese adolescents, prediabetes is often a transient state, with as many as 60% of individuals reverting to normal glucose tolerance within 2 yr. Persistent weight gain is a predictor of persistent prediabetes and progression to diabetes (43).
- Prediabetes is diagnosed when:
 - IFG: FPG is 5.6–6.9 mmol/L (100–125 mg/dL)
 - IGT: Postchallenge plasma glucose 7.8–11.1 mmol/L (140–199 mg/dL)

- HbA1c 5.8–6.4%
 - Must utilize a laboratory based, DCCT aligned, National Glycohemoglobin Standardization Program certified methodology.

Treatment of youth-onset T2D

1 Management differences between T1D and T2D

The emergence of T2D in children and adolescents has required that specialists familiar with the management of T1D in children and adolescents recognize the vast differences between the treatment challenges of these two disorders.

- Differences in socioeconomic status: While T1D is distributed throughout the population proportionate to socioeconomic distribution, T2D in developed countries disproportionately affects those with fewer resources, e.g., lower income levels, less educated parents, less well-insured (35). Conversely, in Asia and emerging economies, T2D disproportionately affects the affluent.
- Older age: T1D occurs throughout childhood, when parental influence is predominant, whereas T2D occurs typically in adolescence, when peer influence predominates.
- More family experience: Only 5% of families with a child with T1D have family experience with the disease, whereas more than 75% of families of the child with T2D have such experience. The failure of these family members to control weight and glycemia is common, with resultant complications in the family members and risk for a sense of helplessness.
- Prevalence of associated comorbidities and complications early in the course of disease: Unlike T1D, where diabetes-related complications develop after many years of diabetes, the majority of patients with T2D will have comorbidities, such as fatty liver, sleep apnea, hypertension (35) at the time of diagnosis and appear to develop microvascular and macrovascular complications at an accelerated rate. Therefore, the treatment of these associated disorders is often required at the time of initiation of therapy for dysglycemia. Reduction in the rate of complications may require especially diligent attention to comorbidities (21, 23, 44, 45).
- Lifestyle education: While education on diet and physical activity is important on all youth with diabetes, the need for intensive lifestyle intervention is a dominant feature of therapy in youth with T2D.

2 Management goals

- Education for diabetes self-management

- Normalization of glycemia
- Weight loss
- Reduction in carbohydrate and calorie intake
- Increase in exercise capacity
- Control of comorbidities, including hypertension, dyslipidemia, nephropathy, sleep disorders, and hepatic steatosis.

3 Education [See also the ISPAD Clinical Practice Guidelines for diabetes education (46)]

Initial and on-going education for T2D should focus on behavioral changes (diet and activity), as well as education on administration of oral hypoglycemic agents and insulin as needed. The materials used to provide diabetes education in the TODAY trial were specifically designed to be age and culturally appropriate for North American populations and are available for public use on the TODAY public website [portal.bsc.gwu.edu/web/today].

- The education and treatment team for T2D ideally should include a nutritionist, psychologist and/or social worker, and exercise physiologist (46).
- Education in T2D places greater emphasis on behavioral, dietary, and physical activity changes than is generally required for T1D.
- Education should be given by team members with expertise and knowledge of the unique dietary, exercise, and psychological needs of youth with T2D.
- Education should be provided in a culturally sensitive and age-appropriate manner.
- Because nearly all youth with T2D are adolescents, the ISPAD Guidelines for Adolescent Care are appropriate to the education of youth and families with T2D.
- The entire family will need education to understand the principles of treatment of T2D and to understand the critical importance of the lifestyle changes required for the entire family to successfully manage a youth with T2D.
- Care providers should acknowledge that the initial uncertainty in the diagnosis of diabetes type in some patients can be confusing and anxiety provoking for the youth and family. The anxiety can be minimized by emphasizing the importance of normalizing blood glucose metabolism using whatever therapy is appropriate to the metabolic circumstances of the specific individual, regardless of the ‘type’ of diabetes.

4 Behavioral change

Lifestyle change is the cornerstone of treatment of T2D and clinicians should initiate a lifestyle modification program, including nutrition and physical activity,

for children and adolescents at the time of diagnosis of T2D (47). The interventions include promoting a healthy lifestyle through behavior change, including nutrition, exercise training, weight management, and smoking cessation. Lifestyle intervention can have a beneficial effect on the incidence of diabetes in patients with impaired glucose tolerance and effectively decrease the incidence of T2D in high-risk patients (48, 49).

- The family and child should understand the medical implications of obesity and T2D.
- Clinicians must have an understanding of the health beliefs and behaviors of the family/community to design an effective behavioral plan.
- Changes should be made in small achievable increments and with the understanding that these changes need to be permanent.
- The patient and family should be trained to monitor the quantity and quality of food, eating behavior, and physical activity on a regular basis.
- As in any behavioral change, a dynamic and sustainable reward system is essential for success.

5 Dietary management

Involvement of a nutritionist/dietitian with knowledge and experience in nutritional management of youth with diabetes is necessary and experience with the unique characteristics of youth with T2D is desirable. Dietary recommendations should be culturally appropriate, sensitive to family resources, and should be provided to all caregivers. The family should be encouraged to make dietary changes consistent with healthy eating recommendations, including individualized counseling for weight reduction, reduced carbohydrate and total and saturated fat intake, increased fiber intake, and increased physical activity (50). More specific dietary recommendations are given in the ISPAD Guidelines for dietary management.

Dietary modification should include:

- Initial focus on eliminating sugar-containing soft drinks and juices. Complete elimination of these drinks and substitution of water, diet soft drinks, and other calorie-free beverages can result in substantial weight loss (51). Food and Drug Administration (FDA)-approved non-nutritive sweeteners (NNS) may help consumers limit carbohydrate and energy intake as a strategy to manage blood glucose or weight (52).
- Increasing fruit and vegetable intake (53).
- Reducing the use of processed, prepackaged, and convenience food.
- Reducing the intake of foods made out of refined, simple sugars such as processed candy and high fructose corn syrup.

- Portion control. Food and snacks should be served in a plate or bowl and not eaten directly from a box or can.
- Reducing meals eaten away from home.
- Asian diets that primarily consist of high-carbohydrate meals, and in some regions, high animal protein intake should be modified, with increased portions of fresh vegetables and decreased portions of carbohydrate-rich noodles, white rice, and starches.
- Changing staple foods from enriched white rice and white flour to brown rice and whole grain items to lower glycemic index and promote gradual and sustainable energy elevations with meals.
- Changing family diet behaviors:
 - Limiting availability of high-fat, high caloric density food and drink in the home.
 - Teaching families to interpret nutrition fact labels.
 - Emphasizing healthy parenting practices related to diet and activity by promoting parental modeling of healthy eating habits and avoiding overly restricted food intake.
 - Encouraging positive reinforcement of all goals achieved (e.g., no or minimal weight gain, reduction in high caloric drinks) and avoiding blame for failure.
 - Promoting that meals should be eaten on schedule, in one place, preferably as a family unit, and with no other activity (television, computer, studying).
 - Collaboration with the family to take into account cultural food preferences and the use of food during family events and cultural festivals.
 - Maintaining food and activity logs as beneficial for raising awareness of food and activity issues and for monitoring progress.

6 Exercise management

Exercise is an important part of the diabetes management plan. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being (54–56). Youth with T2D should be encouraged to engage in moderate-to-vigorous exercise for at least 60 min daily; this can be completed in several shorter segments. Specific, negotiated and enjoyable exercise prescriptions should be developed for each patient and family that are sensitive to family resources and environment. A family member or friend should be identified who is available to participate in physical activity with the patient.

Exercise management should include:

- Collaborative development of an achievable daily exercise program to break the entrenched sedentary lifestyle characteristic of youth with T2D.

- Reduction in sedentary time, including TV, computer-related activities, texting, and video games (57). Screen time should be limited to <2 h a day. Use of electronic entertainment and communication devices (EECDs) such as video games, computers, and smart phones are associated with shortened sleep duration, excess body weight, poorer diet quality, and lower physical activity levels (57–59).
- Promotion of stable household routines, particularly increasing sleep duration and reducing TV viewing (59–61).
- Addressing sedentary time spent doing school work and identifying ways to incorporate physical activity as breaks.
- Promotion of physical activity as a family event, including daily efforts to be physically more active, such as using stairs instead of elevators, walking or bicycling to school and to shop, and doing house and yard work.
- Encouragement of positive reinforcement of all achievements and avoidance of shaming.

7 Smoking and tobacco use.

While cigarette smoking is harmful to all youth, those with special healthcare needs are especially vulnerable to the negative health consequences of smoking as a result of their compromised health status and disease, as well as treatment-related complications (62).

Additional research is needed to develop and examine the efficacy of interventions specifically targeting smoking among youth with T2D within healthcare settings. Patients should be asked at each visit if they are smoking and counseled against initiation of smoking. Those youth who are smoking should be counseled on the importance of smoking cessation and provided resources for support.

8 Glycemic monitoring

- SMBG
 - Unlike in T1D, the evidence that SMBG has an impact on glycemic control in the individual with T2D is limited.
 - SMBG should be performed regularly. The frequency of SMBG should be individualized, and include a combination of fasting and postprandial glucose measurements with a frequency based on the degree of glycemic control and available resources.
 - Once glycemic goals have been achieved, limited at home testing is needed and, at most, a few fasting and postprandial values a week are satisfactory. If values rise out of the target range consistently,

more frequent testing should be recommended for possible need for change in therapy.

- During acute illness or when symptoms of hyper- or hypoglycemia occur, patients should perform more frequent testing and be in contact with their diabetes care team for advice.
- Patients on insulin or sulfonylureas need to monitor for asymptomatic hypoglycemia.
- HbA1c concentration should be determined at least twice a year and quarterly if insulin is being used or metabolic control is unsatisfactory.

9 Pharmacologic therapy (see Fig. 1)

The aim of therapy in youth-onset T2D is to decrease insulin resistance, increase endogenous insulin secretion, or provide exogenous insulin. While a number of oral hypoglycemic agents are available and approved for use in adults, only metformin and insulin are approved for use in youth in the majority of countries. Sulfonylureas are approved for use in adolescents in some countries; other oral agents are described below for information, recognizing that some adolescents may benefit from their use. However, they are generally more expensive than the core therapies and evidence for their use in youth is limited to non-existent at this time. Several clinical trials of newer oral hypoglycemic agents are underway in youth-onset T2D, but are recruiting slowly and results are not expected for many years.

• Initial treatment

Initial treatment of youth with T2D should include metformin and/or insulin alone or in combination. The specifics of the initial treatment modality are determined by symptoms, severity of hyperglycemia, and presence or absence of ketosis/ketoacidosis. As in T1D, those with symptoms, particularly vomiting, can deteriorate rapidly and need urgent assessment and treatment.

- If the patient is metabolically stable (HbA1c < 9 and no symptoms), metformin monotherapy is the treatment of choice. Begin with 500 mg daily × 7 d. Titrate by 500 mg once a week over 3–4 wk until the maximal dose of 1000 mg BID (or 2000 mg once a day of extended release metformin product where available) is reached.
- If the patient is not metabolically stable, insulin will be required at least initially. A variety of insulin regimens are effective, but once a day NPH or basal insulin (0.25–0.5 units/kg starting dose) is often effective in attaining metabolic control, while entailing minimal patient burden and being

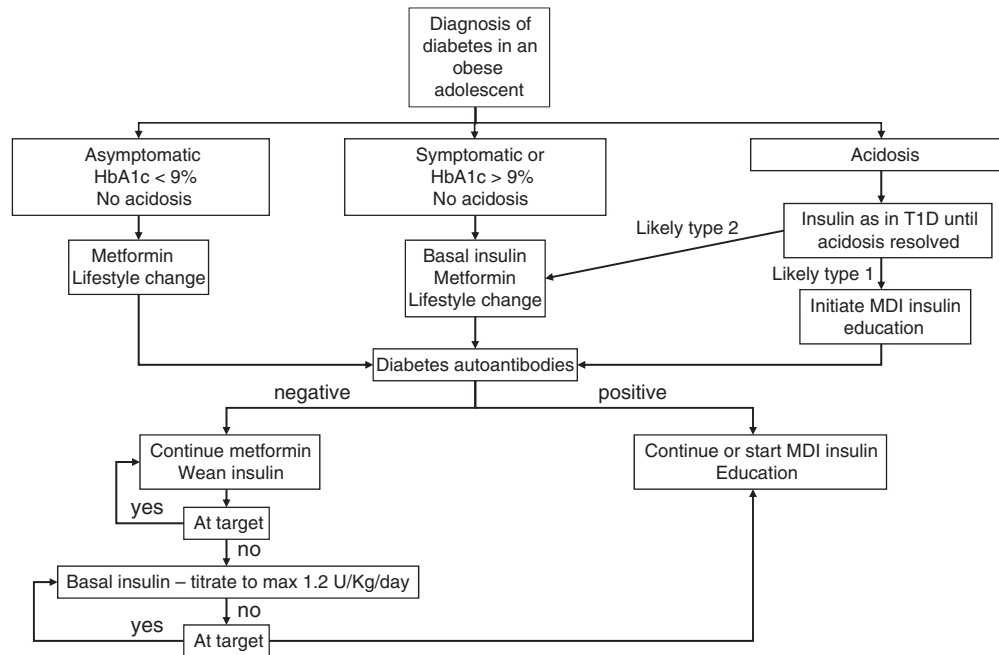


Fig. 1. Approach to initial and subsequent treatment of youth with type 2 diabetes.

well tolerated by the patients. Metformin can generally be started at the same time as metformin, unless acidosis is present.

- Transition onto metformin monotherapy can usually be achieved safely over 2–6 wk by decreasing the insulin dose 30–50% each time the metformin is increased with a goal of eliminating insulin therapy. Data from the TODAY study indicate that 90% of youth with T2D can be successfully treated initially with metformin alone (34)
- If the glucose values remain in the diabetic range during titration of metformin and insulin, the diagnosis of T2D should be reconsidered and lifestyle changes reinforced.

The goal of initial treatment should be to attain HbA1c of <6.5%. This can almost always be accomplished with metformin and basal insulin, alone or in combination. If SMBG values remain in the diabetic range during titration, or the patient fails to reach HbA1c below 6.5%, the diagnosis of T2D should be reconsidered and the need for intensification of therapy should be assessed.

Subsequent therapy

Long-term glycemic control is more likely when therapy is intensified to maintain the HbA1c target (treat-to-target) rather than waiting for the HbA1c to rise before intensifying therapy (treat-to-failure) (63).

- If the patient fails to reach target HbA1c of <6.5% within 3–4 months on metformin monotherapy,

addition of basal insulin should be strongly considered.

- If target is not attained on combination metformin and basal insulin (up to 1.2 U/kg), prandial insulin should be initiated and titrated to reach target HbA1c < 6.5%.
- Use of other oral or injected agents in youth may be beneficial in addition to or instead of metformin and insulin, but there are very limited studies of the use of these agents and they are generally not approved in the population.

Metformin. Metformin acts through adenosine monophosphate (AMP) kinase in liver, muscle, and fat tissue, with a predominant action on the liver.

- Hepatic glucose output is reduced by decreased gluconeogenesis.
- Insulin stimulated glucose uptake is increased in muscle and fat.
- An initial anorexic effect may promote limited weight loss.
- There is little to no risk of hypoglycemia with metformin monotherapy.
- Long-term use is associated with a 1–2% reduction in HbA1c.
- Intestinal side effects (transient abdominal pain, diarrhea, and nausea) may occur. These can be eliminated in most patients with slow dosage titration over 3–4 wk, and instructions to always take the medication with food. The side effects may be attenuated by the use of extended release formulations.

- The risk of lactic acidosis with metformin is extremely low. Metformin should not be given to patients with renal impairment, cardiac or respiratory insufficiency, or who are receiving radiographic contrast materials. Metformin should be temporarily discontinued during a gastrointestinal illness.
- Metformin may normalize ovulatory abnormalities in girls with polycystic ovarian syndrome (PCOS) (ovarian hyperandrogenism) and increase pregnancy risk.
- Metformin is now approved for use during pregnancy.

Insulin. Despite hyperinsulinemia and insulin resistance, supplemental insulin is generally effective in reducing hyperglycemia and attaining glycemic targets. If there is inadequate glycemic control on oral agents, a long-acting (basal) insulin analog without peak effects or once-daily NPH may provide satisfactory therapy without the burden of meal-related injections (64). Metformin should be continued to improve insulin sensitivity and the combination of metformin and once daily insulin is successful at maintaining target glycemia in the majority of youth for extended periods of time. However, if HbA1c target is not reached and postprandial hyperglycemia persists, rapid or short-acting insulin can be added.

The primary adverse effects of insulin are:

- Hypoglycemia: hypoglycemia is very uncommon in youth with T2D despite sometimes very elevated dose of insulin (65).
- Weight gain: weight gain can be substantial in this population when insulin therapy is initiated unless there is careful attention and adherence to dietary measures. Emphasis on diet and exercise is extremely important.

Other available agents. Sulfonylurea and meglitinide/repaglinide (may not be approved for use in those <18 yr in all countries)

- These agents bind to receptors on the K⁺/ATP channel complex causing K⁺ channels to close, resulting in insulin secretion. Meglitinide and repaglinide bind to a separate site on the K⁺/ATP channel complex.
 - Sulfonylurea sites equilibrate slowly and binding persists for prolonged periods; thus, traditional sulfonylureas have prolonged effects.
 - Meglitinide/repaglinide has an intermediate equilibration and binding duration and are prescribed to rapid enhancement of insulin secretion before meals.

- Use of sulfonylureas in adults is associated with a 1.5–2% decrease in HbA1c.
- The major adverse effects of sulfonylureas are:
 - Hypoglycemia: may be severe and prolonged depending on the agent used. Hypoglycemia appears to be more common in youth-onset T2D.
 - Weight gain.
- There has been a single pediatric clinical trial of a sulfonylurea (glimepiride), which showed no superior efficacy to metformin and a greater degree of weight gain and hypoglycemia (66).
- Sulfonylureas may accelerate the loss of beta-cell function and eventual loss of control on oral therapy alone (63).

Thiazolidinedione (TZD) (not approved for use in those <18 yr of age)

TZDs increase insulin sensitivity in muscle, adipose, and liver tissue, with a greater effect on muscle glucose uptake than biguanides. TZDs bind to nuclear peroxisome proliferator activator receptors (PPAR gamma), which are ubiquitous orphan steroid receptors particularly abundant in adipocytes. This activation ultimately increases the formation of proteins involved in the nuclear-based actions of insulin, including cell growth, adipose cell differentiation, regulation of insulin receptor activity, and glucose transport into the cell. The binding of the thiazolidinediones to PPAR gamma receptors is ubiquitous, affecting muscle cell growth and migration in response to growth factors, including arterial walls smooth muscle.

- Long-term treatment in adults is associated with a reduction in HbA1c of 0.5–1.3%.
- There has been a randomized clinical trial of rosiglitazone, but the results have never been published.
- In the TODAY study, addition of rosiglitazone to metformin decreased the risk of progression to insulin requirement by 23% (22).
- Different TZDs have differing effects on lipid profiles, with pioglitazone having a more beneficial effect on LDL than rosiglitazone.
- The side effects of TZDs include weight gain, anemia, and fluid retention (including congestive heart failure) (67, 68). Liver toxicity associated with earlier members of this family has not been found with the newer TZDs.
- Rosiglitazone was under substantial marketing restriction in the USA and Europe due to concerns for an increased risk for congestive heart failure and myocardial infarction (68, 69).
- Although these restrictions have now been lifted, the future of TZDs in therapy for T2D in adults or youth remains unclear.

α-Glucosidase inhibitors (not approved for use in those <18 yr of age)

α-glucosidase inhibitors (acarbose, miglitol) reduce the absorption of carbohydrates in the upper small intestine by inhibiting breakdown of oligosaccharides, thereby delaying absorption in the lower small intestine. This reduces the postprandial rise of plasma glucose.

- Long-term therapy is associated with 0.5–1% reduction in HbA1c (70).
- Because of their mechanism of action, these agents have been particularly widely used and successful in emerging economies where carbohydrates make up a substantial part of the diet.
- There have been no trials of α-glucosidase inhibitors in youth.
- The frequent side effect of flatulence makes these agents unacceptable to most adolescents.

Incretin mimetics [glucagon-like peptide-1 (GLP-1) receptor agonists] (not approved for use in those <18 yr of age)

GLP-1 is rapidly secreted by L-cells in the small intestine into the circulation in response to food, increasing insulin secretion proportionate to BG concentrations, suppressing glucagon, prolonging gastric emptying, and promoting satiety. They are rapidly degraded by dipeptidyl peptidase-IV (DPP-IV); both native GLP-1 and the injected mimetic have a serum half-life of 2 min. In recent years, pharmaceutical alterations in the GLP-1 agonists have resulted in longer acting agents.

- Incretin mimetics are given as BID, once daily, or once-weekly subcutaneous injections.
- Clinical trials in adults have shown reduced fasting and postprandial BG, weight loss, and lower HbA1c (0.5–0.8%).
- Adverse effects include nausea, vomiting, diarrhea, and infrequent dizziness, headache, and dyspepsia. The side effects generally decrease over time.
- There have been no published studies of incretin mimetics in youth, but several are currently underway.

DPP-IV inhibitors (not approved for use in those <18 yr of age)

DPP-IV inhibitors inhibit the enzyme that breaks down GLP-1, resulting in higher concentrations of GLP-1 and effects similar to those of GLP-1 mimetics.

- DPP-IV inhibitors are administered orally once daily.
- Long-term therapy in adults is associated with 0.5% reduction in HbA1c.

- Unlike GLP-1 mimetics, they have no effect on gastric emptying, satiety, or weight loss.
- There have been no published studies of DPP-IV inhibitors in youth, but several are currently underway.

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors (not approved for use in those <18 yr of age)

SGLT-2 inhibitors inhibit renal tubular reabsorption of glucose, leading to increased urinary glucose loss, reduction in serum glucose, and weight loss. The first of these agents have been approved for use in T2D in adults.

- Short-term use of SGLT-2 inhibitors is associated with reduction in HbA1c approaching that seen with metformin. There have been no long-term studies of HbA1c reduction.
- Weight loss in the range of a few kilograms has been reported in short-term studies.
- Adverse effects include small increases in prevalence of urinary infections, particularly among uncircumcised men.
- There have been no studies of SGLT-2 inhibitors in youth.

10 Gastric surgery

Bariatric surgery may be considered for adolescents with obesity-related comorbidities, including T2D (71), particularly when patients have been unsuccessful with medical therapy alone. Recent results from a large US consortium of pediatric bariatric surgery centers have demonstrated remission of T2D and other comorbidities in nearly all youth, with attainment of HbA1c targets exceeding that seen with medical therapy (72). However, Roux-en-Y gastric bypass, the traditional surgical procedure for weight loss, can have significant morbidity and mortality. Newer techniques, which appear to be safer, include gastric banding and sleeve gastrectomy. Although the morbidity and mortality rates in adults have decreased over the last 5 yr, this treatment is still uncommon in children and should be undertaken only in centers with an established and experienced surgical team and outcome data collection program.

T2D and insulin resistance: comorbidities and complications

Insulin resistance is a physiologic abnormality, defined as an impaired response to the physiologic effects of insulin, including effects on glucose, lipid, protein metabolism, and on vascular endothelial function. Insulin resistance can occur in many tissues, including hepatic, muscle, and adipose tissue, and in

some areas of the brain. However, not all tissues are insulin resistant, as some tissues continue to respond to hyperinsulinemia, such as the ovary and the sympathetic nervous system innervating muscle. Finally, within tissues there can be mixed insulin resistance and retained insulin sensitivity, such as the combination of hepatic resistance to insulin's metabolic effects, resulting in increased hepatic glucose output, yet retained insulin response in suppression of sex hormone-binding globulin production, resulting in increased free sex steroids and in stimulation of insulin-like growth factor 1 (IGF-1) production, resulting in mitogenic effects (73).

Insulin resistance is increased during mid-puberty, pregnancy, aging, and the luteal phase of the menstrual cycle, in those of non-Caucasian race/ethnicity, and in those with increased total and visceral adiposity, high fat diet, and sedentary behavior.

Several events in development may be associated with increased risk of the insulin resistance syndrome. Premature adrenarche (pubic hair appearing before the age of 8 yr) in girls may be the first signs of hyperandrogenism as a component of PCOS, a disorder associated with insulin resistance (74, 75). Children born small for gestational age (SGA) are at increased risk of insulin resistance related to decreased intrauterine growth, pancreatic development, and lean muscle mass and are also at increased risk of premature adrenarche. Infants born to a pregnancy complicated by maternal obesity, and in particular maternal T2D or gestational diabetes, are more likely to be born large for gestational age (LGA) and to have an increased risk of insulin resistance (76). The development of obesity and inactivity during childhood also increases the likelihood of insulin resistance.

The insulin resistance syndrome is a collection of abnormalities that are increased in prevalence in insulin-resistant individuals. These abnormalities include:

- Dysglycemia (impaired fasting glucose, impaired glucose tolerance, T2D)
- Lipid abnormalities (increased triglycerides, decreased HDL-C, small, dense LDL-C particles)
- Endothelial dysfunction (increased mononuclear cell adhesion, plasma cellular adhesion molecules and asymmetric dimethylarginine, decreased endothelial-dependent vasodilatation)
- Increased procoagulant factors (plasminogen activator inhibitor-1 and fibrinogen)
- Hemodynamic changes (increased sympathetic nervous system activity, increased renal sodium retention)
- Inflammation [increased C-reactive protein, white blood cells (WBCs), etc.]
- Increased plasma uric acid

- Increased hepatic and intramyocellular lipid deposition
- Mitochondrial dysfunction
- Ovarian hyperandrogenism
- Sleep-disordered breathing.

As a result of these insulin resistance-related abnormalities, individuals with insulin resistance have a higher risk of developing overt T2D, cardiovascular disease, hypertension, PCOS, NAFLD, nephropathy, OSA, and some types of cancer. This recognition that insulin resistance is associated with a cluster of abnormalities differs from the concept of the metabolic syndrome (MetS), which are five specific insulin resistance-related criteria (obesity, elevated BP, impaired fasting glucose, high triglycerides, low HDL-C) chosen originally by the Adult Treatment Panel III, based on increased risk of cardiovascular disease in adults (77).

In contrast to the definition of MetS in adults, there is still no standard definition of MetS for use in the pediatric population and more than 46 different pediatric MetS definitions have been used (78). In 2007, the International Diabetes Federation published its definition of the MetS in children and adolescents (79). This panel recommends the following criteria:

- 1 For children 6 to <10 yr old, obesity (defined as ≥ 90 th percentile of waist circumference), followed by further measurements as indicated by family history.
- 2 For age 10 to <16 yr, obesity (defined as waist circumference ≥ 90 th percentile), followed by the adult criteria for triglycerides, HDL-C, BP, and glucose. For youth ≥ 16 yr of age, the panel recommends using the existing International Diabetes Federation criteria for adults.

When this definition is used, MetS is rapidly increasing in prevalence with rising childhood obesity and sedentary lifestyles worldwide. In western countries, the incidence of childhood obesity has more than doubled over the past generation. Studies show that the prevalence of MetS in obese youth ranges from 19 to 35%, compared with <2% in the normal-weight groups. The odds of developing MetS in obese boys and girls were 46–67 and 19–22 times greater, respectively, than for normal-weight youth (80).

Co-morbidities characteristic of insulin resistance are commonly present at diagnosis or appear early in the course of T2D and should be screened for sooner than in T1D, where these disorders are generally seen as complications of long-standing diabetes rather than as comorbid conditions (81–83). A more complete discussion of screening for complications/comorbidities is presented in the ISPAD Guidelines for microvascular and macrovascular complications (84).

Obesity

Obesity has deleterious associations with morbidity independent of insulin resistance and diabetes (85–94). In addition, weight loss and exercise both improve insulin resistance and glycemia. Shifts up or down in BMI category during childhood are associated with increases and decreases in cardiovascular risks markers (95), and youth in the USA with T2D have a mean BMI Z-score of 2.15 (35). Therefore, the assessment of BMI and pattern of weight gain should be considered a routine part of monitoring in youth with T2D.

Hypertension

Hypertension is associated with endothelial dysfunction, arterial stiffness, and increased risk of both cardiovascular and kidney disease (96). Moreover, tight BP control in adults with T2D in the UK Prospective Diabetes Study (UKPDS) improved microvascular and macrovascular disease at least as much as control of glycemia (97). Hypertension was present in 13.6% of 699 US youth in the TODAY study at a median duration of diabetes of 7 months (35) progressing to 33.8% during average follow-up of 3.9 yr (23). Male sex and higher BMI significantly increased the risk of hypertension in the TODAY cohort. Eppens et al. (98) reported even higher rates in Australia, with 36% of youth with T2D having hypertension within 1.3 yr of T2D diagnosis. Moreover, the SEARCH for Diabetes in Youth Study (SEARCH) study, which included US youth with longer diabetes duration, found hypertension in 65% of US youth with T2D (99, 100). Hypertension in T2D is related to renal sodium retention and resulting volume expansion, increased vascular resistance related to reduced nitric-oxide-mediated vasodilatation and increased sympathetic stimulation by hyperinsulinemia. In addition, there is a possible genetic predisposition to hypertension in T2D related to the associated angiotensin converting enzyme genotype and resulting increased activity of the renin-angiotensin system (101).

- BP should be measured with an appropriate sized cuff at every clinic visit, and normalized for sex, height, and age.
- Initial treatment of BP consistently at, or above, the 95th percentile on three occasions should consist of efforts at weight loss, limitation of dietary salt, and increased physical activity.
- If, after 6 months, BP is still above the 95th percentile, initiation of an ACE inhibitor should be considered to achieve BP values that are less than the 90th percentile (102).
 - Of note, major congenital malformations have been reported with first trimester exposure to ACE inhibitors in non-diabetic women.

- If the ACE inhibitor is not tolerated due to adverse effects (mainly cough), an angiotensin receptor blocker is often used as second line therapy (47, 102–105).
- Combination therapy may be required if hypertension does not normalize on single agent therapy, and may include calcium channel blockers or diuretics.
- Work-up of the hypertension should also include a renal ultrasound and an echocardiogram (96).

Nephropathy

Albuminuria (either micro- or macro-) is present at the time of diagnosis in a substantial number of adolescents with T2D and prevalence increases with duration of diabetes (24). In the TODAY study, microalbuminuria was found in 6.3% of 699 T2D youth at baseline at a median disease duration of 7 months and prevalence rose to 16.6% by 36 months (23, 35); higher levels of HbA1c were significantly related to risk of developing microalbuminuria. Similar findings have been reported in smaller studies of US minority and Indian, Canadian First Nation and Maori youth (15, 106) and macroalbuminuria was reported in 16% of First Nation youth after 10 yr (107, 108). In a study in Manitoba, Canada, those with microalbuminuria as youth were nine times as likely to develop renal failure as those without microalbuminuria (109). Thus, the presence of albuminuria in youth was highly predictive of the future risk of renal failure. The prevalence of micro- and macroalbuminuria is higher and the progression of nephropathy is accelerated in youth-onset T2D compared to T1D in all populations examined. In a Japanese cohort of 1065 patients diagnosed with T2D prior to age 30 yr, 31 (3%) developed renal failure requiring dialysis at a mean age of 35 yr (110). Factors influencing progression were diabetes duration, HbA1c, and diastolic BP. Moreover, the incidence of nephropathy for those diagnosed at age 10–19 yr was double that of individuals in the same population with T1D, even when accounting for duration of disease (111).

- Micro- and macroalbuminuria may be present at the time of diagnosis.
- Albuminuria should be evaluated at diagnosis and annually thereafter.
- The definition of microalbuminuria used by the ADA is either:
 - Albumin-to-creatinine ratio 30–299 mg/g in a spot urine sample (preferred).
 - Timed overnight or 24-h collections with albumin excretion rate of 20–199 mcg/min.
- An elevated value can be secondary to exercise, smoking, menstruation, and orthostasis. Therefore,

the diagnosis of persistent abnormal microalbumin excretion requires documentation of two of three consecutive abnormal values obtained on different days.

- Repeat testing should be done in the AM immediately after rising, as orthostatic proteinuria is common in adolescents and is considered benign.
- Non-diabetes-related causes of renal disease should be excluded and consultation obtained, especially if macroalbuminuria (ACR > 300 mg/g) is present.
- ACE inhibitors are the agents of choice because of the beneficial effects of ACE inhibitors on preventing diabetic nephropathy, even if BP is normal (2).
- Albumin excretion should be monitored at 3- to 6-month interval and therapy titrated to achieve as normal an albumin-to-creatinine ratio as possible.

Dyslipidemia

Hypertriglyceridemia and decreased HDL-C are the hallmarks of the dyslipidemia characteristic of insulin resistance and T2D. In the TODAY study, 79.8% of T2D youth had a low HDL-C and 10.2% had high triglycerides within a few months of diagnosis (35) and the SEARCH study found that 73% of 2096 US youth with T2DM of longer duration had a low HDL and 60–65% had hypertriglyceridemia (112). Among Pima Indians in the US, 18% had evidence of hypercholesterolemia at T2D diagnosis (107). In a Canadian First Nations population of 99 youth with T2D, total cholesterol, LDL-C, triglycerides, and apoB level greater than the NHANES 75th percentile were found in 60, 41, 43, and 43%, respectively, and low HDL-C in 35% (108). In 68 Australian youth with a duration of T2D of <3 yr, elevated total cholesterol was found in 32% and hypertriglyceridemia in 53% (98). Finally in Taiwan, hypercholesterolemia was present in 27% youth with T2D (11). Additional findings include elevated very low-density lipoprotein (VLDL), elevated lipoprotein (a) (Lp_a), and increased small dense LDL-C particles. Decreased lipoprotein lipase activity, increased lipoprotein allocation, and increased lipoprotein oxidation render the lipoproteins more atherogenic.

- Testing for dyslipidemia should be performed soon after diagnosis when blood glucose control has been achieved and annually thereafter (113–115).
- Goal levels are:
 - LDL-C <2.6 mmol (100 mg/dL)
 - HDL-C >35 mg/dL (0.91 mmol/L)
 - Triglycerides <150 mg/dL (1.7 mmol/L)

- If LDL-C is above goal, blood glucose control should be maximized and dietary counseling should be provided using the AHA step 2 diet (dietary cholesterol <200 mg/d, saturated fat <7% of total calories, and <30% calories from fat) and exercise encouraged (114).
- A repeat lipid profile should be performed in 6 months.
 - If LDL-C remains elevated, further intervention is warranted:
 - LDL-C 100–129 mg/dL: maximize non-pharmacologic treatment.
 - LDL-C >130 mg/dL: begin medication with a goal of <130 mg/dL and an ideal target of <100 mg/dL
- Statin therapy has been shown to be safe and effective in children as in adults and should be the first pharmacologic intervention (84), although long-term safety data are not available.
- Statin treatment should begin at the lowest available dose and dose increases should be based on LDL-C levels and side effects.
- If there is any persistent complaint of significant muscle pain/muscle soreness, the medication should be discontinued to see if symptoms resolve.
- The use of statins in sexually active adolescent females must be very carefully considered and the risks explicitly discussed, as these drugs are not approved in pregnancy.
- Current recommendations are to not manage elevated triglyceride levels directly with medication for cardiovascular disease prevention.
- If the triglycerides are >150 mg/dL, efforts to maximize blood glucose control, limit dietary fat and simple sugars, and achieve desirable weight should be emphasized.
- If fasting triglycerides are >400–600 mg/dL, treatment with a fibric acid medication should be considered due to significantly increased risk of pancreatitis, with a goal of <150 mg/dL.
- Low HDL-C levels in youth are not managed directly with medication, but physical activity and healthy diet should be encouraged.

Atherosclerosis and vascular dysfunction

Hyperglycemia, dyslipidemia, and hypertension are contributors to the acceleration of atherosclerosis in T2D, along with oxidative stress, glycation of vascular proteins, and abnormalities in platelet function and coagulation. Defective endothelium-dependent vasodilatation is an additional factor accelerating atherosclerosis in T2D. Endothelial dysfunction is an

early sign of increased risk of cardiovascular disease, is predictive of cardiovascular events (81) and occurs in obese children relative to their level of obesity and degree of insulin resistance. In addition, youth with T2D have left ventricular hypertrophy (116), cardiac dysfunction, reduced maximal exercise capacity (41), and increased arterial stiffness (117) all of which predict early cardiovascular morbidity and mortality.

Polycystic ovarian syndrome

PCOS is increasingly recognized in adolescents as part of the insulin resistance syndrome. Adolescents with PCOS have ~40% reduction in insulin-stimulated glucose disposal compared to body composition matched non-hyperandrogenic control subjects (118). There are limited data on the exact prevalence of PCOS in youth with T2D, but a study of 157 adult women of reproductive age with T2D found the PCOS prevalence to be high at 8.3% (119). A lack of periods can increase long-term risk of endometrial cancer and PCOS increases lifetime risk of cardiovascular disease (120).

- A menstrual history should be taken on every girl with T2D at diagnosis and at each visit.
- A work-up for PCOS should be considered if there is primary or secondary amenorrhea, hirsutism, and significant acne.
- PCOS is diagnosed based on the presence of oligo- or amenorrhea with biochemical or clinical evidence of hyperandrogenism, with or without evidence for polycystic ovaries (121).
- Decreasing insulin resistance with weight loss, exercise and metformin improves ovarian function and increases fertility.
- Girls receiving diabetes treatment should also be counseled that fertility may improve as a result and appropriate birth control should be used when desired to prevent pregnancy.

Non-alcoholic fatty liver disease

Hepatic steatosis is present in 25–50% of adolescents with T2D and more advanced forms of NAFLD, such as non-alcoholic steatohepatitis (NASH), are increasingly common and associated with progression to cirrhosis, portal hypertension, and liver failure (122–124). NAFLD is now the most frequent cause of chronic liver disorders among obese youth (125), and is the most common reason for liver transplantation in adults in USA. In USA, Hispanics have the highest prevalence of NAFLD, followed by non-Hispanic Whites, whereas the prevalence among African-American is much lower (124, 126). However, these prevalence estimates are based on liver enzyme elevations and are likely an under estimate of the prevalence

of hepatic steatosis in T2D youth, as steatosis is more common than elevated liver enzymes and liver enzymes can be normal despite having steatosis (127).

NAFLD is associated with insulin resistance leading to a resistance in the antilipolytic effect of insulin in the adipose tissue with an increase of FFAs. The increase of FFAs induces mitochondrial dysfunction and development of lipotoxicity. Moreover, in subjects with NAFLD, ectopic fat also accumulates in the myocardium and pancreas (128). Presence of the MetS in obese adolescents predicts IGT and NAFLD (41) and the presence of T2D independently predicts progression to fibrosis (129).

Weight loss improves NAFLD and metformin has been shown to improve liver enzymes and liver steatosis in youth in insulin-resistant adolescents (41). In the TODAY study, permanent medication reductions/discontinuation due to elevated liver enzymes was lowest in the metformin plus rosiglitazone group (65). Thus, T2D therapies that improve insulin resistance appear to improve NAFLD, and therefore are the standard approach to youth with both NAFLD and T2D. However, due to the potential for progression to NASH, fibrosis, and cirrhosis, ongoing monitoring of liver enzymes is recommended in youth with T2D, with referral for biopsy if enzymes remain markedly elevated despite weight loss and/or diabetes therapies.

Systemic inflammation

Elevated C-reactive protein, inflammatory cytokines, and WBC counts in obese adolescents have been associated with increased risk of cardiovascular disease in adults (92, 93). Inflammation plays a critical role in the pathogenesis of diabetes-related chronic kidney disease (130), diabetic retinopathy (131), β -cell dysfunction (132, 133), and other diabetes-related diseases. Several inflammatory cytokines secreted by obese adipose tissue, including TNF α and IL-6, impair insulin signaling in insulin-responsive organs, and new molecules that affect both local and systemic inflammation have been identified (134). In addition, a role for activated immune cells is emerging (135, 136).

Obstructive sleep apnea. OSA is common in obese youth, but the prevalence in pediatric T2D has not yet been well documented. However, it is likely high, as the prevalence of OSA in adults with T2D is between 70 and 90% (137, 138). OSA not only causes poor sleep quality and daytime sleepiness, but has clinical consequences, including hypertension, left ventricular hypertrophy, and increased risk of renal and cardiovascular disease.

- The International Diabetes Federation Taskforce on Epidemiology and Prevention strongly recommended that health professionals working in T2D consider the presence of OSA (139).

- OSA can be screened for in youth with T2D using about snoring, sleep quality, apnea, morning headaches, daytime sleepiness, nocturia, and enuresis.
- If symptoms are suggestive, the diagnosis of OSA is made by formal sleep study and referral to a sleep specialist.

Depression

Youth with T2D are at increased risk of major clinical depression (140–144), which is associated with poor adherence to diabetic treatment recommendations. Signs include depressed mood, markedly diminished interest or pleasure, increased or decreased appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, and recurrent thoughts of death.

- Youth with T2D should be assessed for depression at diagnosis and periodically thereafter, particularly in those with frequent emergency department visits or poor glycemic control.
- Identified patients should be referred to appropriate mental healthcare providers experienced in addressing depression in youth (140).

Additional health problems related to obesity and T2D

- Orthopedic problems resulting in diminishing physical activity (145, 146)
- Pancreatitis
- Cholecystitis
- Pseudotumor cerebri
- Deep tissue ulcers

Adults in their 40s with youth-onset T2D have a marked excess of macrovascular disease, with a high prevalence of ischemic heart disease (12.6%), stroke (4.3%), the composite end point of any macrovascular disease (14.4%), and death (11%) (147). In addition, all of these endpoints were markedly higher than a similarly aged group of participants with T1D, despite similar glycemic control and a longer duration of diabetes in the T1D group. It has been estimated that youth and young adults with T2D lose approximately 15 yr from average life expectancy and may experience severe, chronic complications by their 40s (148). Therefore, a comprehensive management plan that includes early and aggressive control of diabetes complications and cardiovascular risk factors is needed to reduce lifetime risk of morbidity and early death

Screening for T2D in high-risk youth

As opposed to identification of diabetes in a specific youth in whom there is a moderate or high level of clinical suspicion for diabetes, screening refers to broad-based testing of a population or testing of individuals meeting certain general criteria. While the former is necessary in the evaluation of individual patients, the latter is only justifiable in certain circumstances (149). General guidelines to justify a screening test and as applied to T2D in youth are as follows:

- The condition tested for is sufficiently common to justify the cost of the testing.
 - It is not clear that this is the case in most populations. In the USA, screening based on fasting and postchallenge glucose in high risk minority adolescents at the peak age of T2D diagnosis identified <1% with T2D (88). Whether there is sufficient prevalence of undiagnosed T2D in specific populations of adolescents to justify testing remains unclear.
 - If the disorder has low prevalence, most abnormal tests will be false positives and require additional testing, which must be included in the determination of cost.
- The condition tested for is serious in terms of morbidity and mortality.
 - Unquestionably true of T2D in adolescents because of the association with increased cardiovascular risk factors and renal dysfunction.
- The condition tested for has a prolonged latency period without symptoms, during which abnormality can be detected and treatment can prevent morbidity.
 - Prediabetes has been identified in at-risk youth, but there is currently no evidence that interventions beyond that which would be delivered to the at-risk youth anyway (weight loss, exercise, and diet change) are efficacious.
 - Hypertension, dyslipidemia, and microalbuminuria have been identified in youth with prediabetes, but also in obese youth without diabetes. Therefore, this argues for monitoring and appropriate treatment of hypertension, dyslipidemia, and microalbuminuria in at-risk youth, not identification of dysglycemia.
- A test is available that is sensitive (few false negatives) and accurate with acceptable specificity (minimal number of false positives).

- None of the currently available tests (fasting glucose, random glucose, 2-h postchallenge glucose, and HbA1c) are sufficiently sensitive and specific to function, given the low prevalence of T2D even in high-risk populations
- There remains substantial uncertainty in the normal ranges and meaning of abnormal values in each of these measures of glycemia.

There are currently a single set of recommendations for screening and case-finding, which were issued by the ADA in 2000. However, concerns about these guidelines persist. Accumulating data indicate that screening to identify diabetes in asymptomatic youth has a low yield and further research is required to determine the optimal strategy for testing, including the frequency of testing. Therefore, for now, the best evidence suggests that screening for T2D outside of research settings is not cost-effective in most populations. Urinary glucose screening in Japanese youth may be a unique exception.

Conflicts of interest

The authors have declared no conflicts of interest.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

The diagnosis and management of monogenic diabetes in children and adolescents

Rubio-Cabezas O, Hattersley AT, Njølstad PR, Mlynarski W, Ellard S, White N, Chi DV, Craig ME.
The diagnosis and management of monogenic diabetes in children and adolescents.
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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- Monogenic diabetes is uncommon, accounting for ~1–4% of pediatric diabetes cases (B).
- All patients diagnosed with diabetes in the first 6 months of life should have immediate molecular genetic testing to define their subtype of monogenic neonatal diabetes mellitus (NDM), as type 1 diabetes is extremely rare in this subgroup (B). In patients diagnosed between 6 and 12 months of age, testing for NDM should be limited to those without islet antibodies as the majority of patients in this age group have type 1 diabetes (B).
- The molecular genetic diagnosis of NDM will give information on which patients have a potassium channel mutation and can be treated with high dose sulfonylureas and which patients have transient

neonatal diabetes mellitus (TNDM), which will resolve but may later relapse. In addition the diagnosis will inform other likely features, e. g., pancreatic exocrine failure and developmental delay (B).

- The diagnosis of maturity-onset diabetes of the young (MODY) should be suspected in cases with:
 - A family history of diabetes in one parent and first degree relatives of that affected parent in patients who lack the characteristics of type 1 diabetes [no islet autoantibodies, low or no insulin requirements 5 yr after diagnosis (stimulated C-peptide >200 pmol/L)] and lack the characteristics type 2 diabetes (marked obesity, acanthosis nigricans).

- Mild stable fasting hyperglycemia which does not progress. Such cases should be tested for glucokinase (*GCK*) gene mutations, which is the commonest cause of persistent, incidental hyperglycemia in the pediatric population (B).
- Specific features can suggest subtypes of MODY, such as renal developmental disease or renal cysts (*HNF1B*-MODY) and macrosomia and/or neonatal hypoglycemia (*HNF4A*-MODY) (C).
- In familial autosomal dominant symptomatic diabetes, mutations in the hepatocyte nuclear factor 1 α (*HNF1A*) gene (*HNF1A*-MODY) should be considered as the first diagnostic possibility, while mutations in the *GCK* gene are the most common cause in the absence of symptoms or marked hyperglycemia (B).
- Results of genetic testing should be reported and presented to families in a clear and unambiguous manner, as results may have a major effect on clinical management (E).
- Referral to a specialist in monogenic diabetes or an interested clinical genetics unit is recommended when predictive testing of asymptomatic individuals is requested (E).
- Some forms of MODY diabetes are sensitive to sulfonylureas, such as *HNF1A*-MODY and *HNF4A*-MODY (B).
- Mild fasting hyperglycemia due to *GCK*-MODY is not progressive during childhood; patients do not develop complications (B) and do not respond to low dose insulin or oral agents (C), so should not receive treatment.

Introduction

Monogenic diabetes results from one or more defects in a single gene. The disease may be inherited within families as a dominant, recessive, or non-Mendelian trait or may present as a spontaneous case due to a *de novo* mutation. Well over 40 different genetic subtypes of monogenic diabetes have been identified to date, each having a typical phenotype and a specific pattern of inheritance.

A familial form of mild diabetes presenting during adolescence or in early adulthood was first described many years ago (1, 2). Even though diabetes presented in young patients, the disease clinically resembled elderly onset non-insulin dependent diabetes and the newly recognized subtype of familial diabetes became known by the acronym MODY (3). As MODY patients passed on the disease to their offspring following an autosomal dominant pattern of inheritance, it was quickly suspected that it might be a monogenic disorder (4). MODY is by far the commonest type of monogenic diabetes. All currently known subtypes of MODY are

caused by dominantly acting heterozygous mutations in genes important for the development or function of β cells (1, 5). Over the last few years, however, a number of forms of monogenic diabetes clinically and genetically different from MODY have been identified (6). Some patients harbor dominant mutations arising *de novo* (i.e., not inherited from parents) so family history suggesting a monogenic condition is lacking (7–9). These facts, along with a widespread lack of awareness, hinder clinical diagnosis so that the majority of children with genetically proven monogenic diabetes are initially misdiagnosed as having type 1 (10–12) or, less commonly, type 2 diabetes (13). Although monogenic diabetes is uncommon, it accounts for 1–4% of pediatric diabetes cases (14–16).

Clinical relevance of diagnosing monogenic diabetes

Identification of children with monogenic diabetes usually improves their clinical care. Making a specific molecular diagnosis helps predict the expected clinical course of the disease and guide the most appropriate management in a particular patient, including pharmacological treatment. Furthermore, it has important implications for the family as it enables genetic counseling and frequently triggers extended genetic testing in other diabetic family members, whose diabetes may eventually be reclassified.

Selecting candidates for molecular testing

In contrast to type 1 and type 2 diabetes, where there is no single diagnostic test, molecular genetic testing is both sensitive and specific for diagnosing monogenic diabetes. Genetic testing is currently available in many countries around the world and should be strongly considered in patients with suspected monogenic diabetes (see below). Appropriate informed consent/assent must be prospectively obtained from the patient and his/her legal guardians. Genetic testing for some conditions is available free of charge on a research basis in certain academic institutions (e.g., www.diabetesgenes.org, <http://monogenicdiabetes.uchicago.edu>, <http://www.pediatrics.umed.pl/team/en/contact>, www.mody.no, and <http://www.euro-wabb.org/en/european-genetic-diagnostic-laboratories>).

Next-generation sequencing enables the simultaneous analysis of multiple genes at a lower cost and may become a feasible alternative to traditional genetic testing in the near future (17–20). In the meantime, a judicious approach to selecting candidates for molecular testing is required. The simplest way of maximizing the cost-effectiveness of traditional genetic testing is by

increasing its positive yield through a reasoned selection of the appropriate gene(s) for analysis according to the patient's clinical, immunological, and/or biochemical phenotype (21, 22). This process may be relatively easy to undertake when clinical features directly pointing to a specific syndrome are present, but results may be very difficult to achieve when diabetes is the only manifestation of the monogenic disorder.

When to suspect a diagnosis of type 1 diabetes in children may not be correct?

Features in children initially thought to have type 1 diabetes that suggest a possible diagnosis of monogenic diabetes are shown below. Except for age of diagnosis less than 6 months, none of these are pathognomonic and should be considered together rather than in isolation:

- 1 Diabetes presenting before 6 months of age as type 1 diabetes is extremely rare in this age-group (2, 23).
- 2 Family history of diabetes in one parent and other first degree relatives of that affected parent.
- 3 Absence of islet autoantibodies, especially if measured at diagnosis.
- 4 Preserved β -cell function, with low insulin requirements and detectable C-peptide (either in blood or urine) over an extended partial remission phase (5 yr after diagnosis).

When to suspect a diagnosis of type 2 diabetes in children may not be correct?

In young people, type 2 diabetes often presents around puberty and the majority are obese. A number of features that should suggest monogenic diabetes are listed below:

- 1 Absence of severe obesity.
- 2 Lack of acanthosis nigricans and/or other markers of metabolic syndrome.
- 3 Ethnic background with a low prevalence of type 2 diabetes, e.g., European Caucasian.
- 4 Strong family history of diabetes without obesity.

Interpretation of genetic findings

Despite the obvious clinical benefits derived from an increased awareness and more widely available genetic diagnostic services, care needs to be exercised in the interpretation of genetic findings (24). The way the clinician interprets the genetic report will have a major effect on the further clinical management of the patient and his/her family. Therefore, it is crucial that the results are presented in a clear and unambiguous way

to ensure that both clinicians and patients receive adequate and understandable information. Specific recommendations describing the information that should be included in the molecular genetics laboratory report for MODY testing have been published (25). These include the method used for mutation screening, whether the mutation is novel and if so, evidence for its pathogenicity, and information about the likelihood of the disease being inherited by the offspring. Referral to a specialist unit (diabetes genetics or clinical genetics) is recommended when predictive testing of asymptomatic individuals is requested.

Specific subtypes of monogenic diabetes and their management

The different forms of monogenic diabetes can be classified according to the main pathogenic mechanism into two separate groups (26): genetic defects of insulin secretion and genetic defects of insulin action. In children, the majority of cases result from mutations in genes causing β cell loss or dysfunction although diabetes can rarely occur from mutations resulting in very severe insulin resistance. From a clinical perspective, clinical scenarios when a diagnosis of monogenic diabetes should be considered include:

- 1 Diabetes presenting before 6 months of age (NDM).
- 2 Autosomal dominant familial mild hyperglycemia or diabetes.
- 3 Diabetes associated with extrapancreatic features.
- 4 Monogenic insulin resistance syndromes.

NDM diabetes diagnosed within the first 6–12 months of life

The clinical presentation of autoimmune type 1 diabetes is exceedingly rare before age 6 months (23, 27). Even though autoantibodies against β -cell antigens may be occasionally found in very young diabetic infants (23), it is now accepted that *FOXP3* mutations, and not type 1 diabetes, will account for most of these cases (28). Therefore, all patients diagnosed under 6 months should have genetic testing for monogenic NDM. Some cases of monogenic diabetes can be diagnosed between 6 and 12 months (12, 29, 30) although the vast majority of these patients have type 1 diabetes.

Many patients with NDM are born small for gestational age, which reflects a prenatal deficiency of insulin secretion as insulin exerts potent growth-promoting effects during intrauterine development (31). Approximately half will require lifelong treatment to control hyperglycemia - permanent neonatal diabetes mellitus (PNDM). In the remaining cases, diabetes will remit within a few weeks or months

- transient neonatal diabetes mellitus (TNDM), although it might relapse later in life. In both situations, diabetes presents more frequently as an isolated condition, but some patients show a variety of associated extra-pancreatic clinical features pointing to a particular gene, which may help guide genetic testing (Table 1).

The genetic basis of TNDM has been mostly uncovered: approximately two thirds of cases are caused by abnormalities in an imprinted region on chromosome 6q24 (32, 33), with activating mutations in either of the genes encoding the two subunits of the ATP-sensitive potassium (K_{ATP}) channel of the β -cell membrane (*KCNJ11* or *ABCC8*) causing the majority of the remaining cases (34). A minority of cases of TNDM is caused by mutations in other genes, including *HNF1B* (35), *INS* (preproinsulin gene) (36), etc. In contrast, the genetic abnormality responsible for up to 30% of PNDM cases remains unknown, although the commonest known cause in outbred populations are mutations in the K_{ATP} channel or *INS* genes (37, 38). If parents are related, Wolcott–Rallison syndrome or homozygous mutations in the *GCK* gene are the most common etiologies (37).

Transient neonatal diabetes from imprinting anomalies on 6q24

Anomalies at the 6q24 locus, spanning two candidate genes *PLAGL1* and *HYMAI*, are the single most common cause of neonatal diabetes and always result in TNDM (39). In normal circumstances, this region is maternally imprinted so that only the allele inherited from the father is expressed. TNDM is ultimately associated with overexpression of the imprinted genes (40), with three different molecular mechanisms identified to date: paternal uniparental disomy of chromosome 6 (either complete or partial; it accounts for 50% of sporadic TNDM cases), unbalanced paternal duplication of 6q24 (found in most familial cases), and abnormal methylation of the maternal allele (found in some sporadic cases) (41). Methylation defects may affect only the 6q24 locus or may arise in the context of a generalized hypomethylation syndrome along with other clinical features including congenital heart defects, brain malformations, etc. (42). Some cases of TNDM secondary to multiple methylation defects are caused by recessively acting mutations in *ZFP57*, a gene on chromosome 6p involved in the regulation of DNA methylation (43).

Patients with 6q24 abnormalities are born with severe intrauterine growth retardation and develop severe but non-ketotic hyperglycemia very early on, usually during the first week of life (41, 44). Despite the severity of the initial presentation, the insulin dose can be tapered quickly so that the majority of patients do

not require any treatment by a median age of 12 wk. One third of patients show macroglossia and, more rarely, an umbilical hernia is present. During remission, transient hyperglycemia may occur during intercurrent illnesses (45). Over time, diabetes relapses in at least 50–60% of patients, usually around puberty, although recurrences have been reported as young as 4 yr of age. Relapse clinically resembles early-onset type 2 diabetes and is characterized by a loss of the first-phase insulin secretion. Insulin therapy is not always necessary (there is usually some response to oral sulfonylureas) and, if needed, insulin doses required tend to be lower than in patients with type 1 diabetes.

The phases described above do not present irretrievably in every patient. Interestingly, some mutation carrier relatives develop type 2 diabetes or gestational diabetes in adulthood without any evidences of having had neonatal diabetes, suggesting that other genetic or epigenetic factors may influence the clinical expression alterations of chromosome 6q24 (32).

The role of genetic counseling depends on the underlying molecular mechanism. Uniparental disomy of chromosome 6 is generally sporadic and therefore the risk of recurrence in siblings and offspring is low. When paternal duplication of the 6q24 region is found, males have a 50% chance of transmitting the mutation and the disease to their children. In contrast, females will pass on the duplication but their children will not develop the disease. In this case, TNDM may recur in the next generation as their asymptomatic sons pass on the molecular defect to their own children. Some methylation defects (i.e., *ZFP57* mutations) show an autosomal recessive inheritance and hence the recurrence risk is 25% for siblings and almost negligible for the offspring of a patient.

Neonatal diabetes due to mutations in the K_{ATP} channel genes

K_{ATP} channels are hetero-octameric complexes formed by four pore-forming Kir6.2 subunits and four SUR1 regulatory subunits, encoded by the genes *KCNJ11* and *ABCC8*, respectively (46). They regulate insulin secretion by linking intracellular metabolic state to the β -cell membrane electrical activity. Any increase in the intracellular metabolic activity induces an increase in the ATP/ADP ratio within the pancreatic β -cell which makes the K_{ATP} channels close, and leads to the cell membrane depolarization which ultimately triggers insulin secretion (47). Activating mutations in *KCNJ11* or *ABCC8*, which prevent K_{ATP} channel closure and hence insulin secretion in response to hyperglycemia, are the most common cause of PNDM (7, 48–51) and the second most common cause of TNDM (34).

The majority of patients with mutations in *KCNJ11* have PNDM rather than TNDM (90 vs. 10%). In

Table 1. Monogenic subtypes of neonatal and infancy-onset diabetes (modified from reference 37)

Gene	Locus	Inheritance	Other clinical features	References
Abnormal pancreatic development				
<i>PLAGL1/HYMAI</i>	6q24	Variable (imprinting)	TNDM ± macroglossia ± umbilical hernia	(33)
<i>ZFP57</i>	6p22.1	Recessive	TNDM (multiple hypomethylation syndrome) ± macroglossia ± developmental delay ± umbilical defects ± congenital heart disease	(43)
<i>PDX1</i>	13q12.1	Recessive	PNDM + pancreatic agenesis (steatorrhea)	(173)
<i>PTF1A</i>	10p12.2	Recessive	PNDM + pancreatic agenesis (steatorrhea) + cerebellar hypoplasia/aplasia + central respiratory dysfunction	(174)
<i>PTF1A</i> enhancer	10p12.2	Recessive	PNDM + pancreatic agenesis without CNS features	(89)
<i>HNF1B</i>	17q21.3	Dominant	TNDM + pancreatic hypoplasia and renal cysts	(35)
<i>RFX6</i>	6q22.1	Recessive	PNDM + intestinal atresia + gall bladder agenesis	(175)
<i>GATA6</i>	18q11.1-q11.2	Dominant	PNDM + pancreatic agenesis + congenital heart defects + biliary abnormalities	(90)
<i>GATA4</i>	8p23.1	Dominant	PNDM + pancreatic agenesis + congenital heart defects	(176)
<i>GLIS3</i>	9p24.3-p23	Recessive	PNDM + congenital hypothyroidism + glaucoma + hepatic fibrosis + renal cysts	(177)
<i>NEUROG3</i>	10q21.3	Recessive	PNDM + enteric anendocrinosis (malabsorptive diarrhea)	(178)
<i>NEUROD1</i>	2q32	Recessive	PNDM + cerebellar hypoplasia + visual impairment + deafness	(179)
<i>PAX6</i>	11p13	Recessive	PNDM + microphthalmia + brain malformations	(180)
<i>MXN1</i>	7q36.3	Recessive	PNDM + developmental delay + sacral agenesis + imperforate anus	(181) (175)
<i>NKX2-2</i>	20p11.22	Recessive	PNDM + developmental delay + hypotonia + short stature + deafness + constipation	(182)
Abnormal β-cell function				
<i>KCNJ11</i>	11p15.1	Spontaneous or dominant	PNDM/TNDM ± DEND	(7)
<i>ABCC8</i>	11p15.1	Spontaneous, dominant or recessive	TNDM/PNDM ± DEND	(48)
<i>INS</i>	11p15.5	Recessive	Isolated PNDM or TNDM	(36)
<i>GCK</i>	7p15-p13	Recessive	Isolated PNDM	(83)
<i>SLC2A2 (GLUT2)</i>	3q26.1-q26.3	Recessive	Fanconi–Bickel syndrome: PNDM + hypergalactosemia, liver dysfunction	(183)
<i>SLC19A2</i>	1q23.3	Recessive	Roger's syndrome: PNDM + thiamine-responsive megaloblastic anemia, sensorineural deafness	(184)
Destruction of β cells				
<i>INS</i>	11p15.5	Spontaneous or dominant	Isolated PNDM	(9)
<i>EIF2AK3</i>	2p11.2	Recessive	Wolcott–Rallison syndrome: PNDM + skeletal dysplasia + recurrent liver dysfunction	(77)
<i>IER3IP1</i>	18q21.2	Recessive	PNDM + microcephaly + lissencephaly + epileptic encephalopathy	(185)
<i>FOXP3</i>	Xp11.23-p13.3	X-linked, recessive	IPEX syndrome (autoimmune enteropathy, eczema, autoimmune hypothyroidism, and elevated IgE)	(186)
<i>WFS1</i>	4p16.1	Recessive	PNDM* + optic atrophy ± diabetes insipidus ± deafness	(126)

CNS, central nervous system; DEND, developmental delay, epilepsy, and neonatal diabetes syndrome; IgE, immunoglobulin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; TNDM; transient neonatal diabetes mellitus.

*The mean age of diagnosis among patients with *WFS1* mutations is approximately 5 yr (129).

contrast, mutations in *ABCC8* cause TNDM more frequently (~66%) (48, 52). There are no significant differences between the two subtypes of neonatal diabetes regarding the severity of intrauterine growth retardation or the age at diagnosis of diabetes (34, 53). Patients with K_{ATP} channel mutations typically show milder intrauterine growth retardation and are diagnosed slightly later than patients with 6q24 abnormalities, indicating a less severe insulin deficiency during the last months of intrauterine development and at the time birth. In K_{ATP} -TNDM patients, diabetes usually remits later and relapses earlier than in 6q24-TNDM (34).

Presenting clinical features in patients with K_{ATP} channel activating mutations suggest insulin dependency, with low or undetectable C-peptide levels and frequent presentation with diabetic ketoacidosis (54). In addition to diabetes, about 20% of patients with mutations in *KCNJ11* were initially found to present with associated neurological features (7, 54, 55) in keeping with the expression of K_{ATP} channels in neurons and muscle cells (47, 56). The most severe defect included marked developmental delay and early-onset epilepsy and became known as DEND (developmental delay, epilepsy, and neonatal diabetes) syndrome. An intermediate DEND syndrome characterized by neonatal diabetes and less severe developmental delay without epilepsy is more common. Neurological features were considered less frequent and usually milder in patients with mutations in *ABCC8* (48, 49). However, a recent study suggested that mild neurodevelopmental abnormalities, including developmental coordination disorder (particularly visual-spatial dyspraxia) or attention deficits, might be found on detailed testing in all patients with K_{ATP} channel mutations (57).

Approximately 90% of patients with activating mutations in the K_{ATP} channel genes can be transferred from insulin onto sulfonylurea tablets (58, 59). Transfer usually improves glycemic control without increasing the risk of hypoglycemia. The doses required are high when calculated on a per kg body weight basis compared with adults with type 2 diabetes, typically needing around 0.5 mg/kg/d of glibenclamide, although doses as high as 2.3 mg/kg/d have been occasionally reported (60, 61). Many patients have been able to progressively reduce the dose of sulfonylurea after transition while maintaining excellent glycemic control (58, 62). The only side effects reported to date are transient diarrhea and staining of the teeth (63, 64). Some brain imaging studies have shown that sulfonylurea drugs may penetrate blood–brain barrier (65, 66) and very interesting case reports suggest that sulfonylureas may partially improve some of the neurological symptoms (67–70).

Activating mutations in *KCNJ11* causing neonatal diabetes are always heterozygous. As about 90% of

these mutations arise *de novo*, there is usually no family history of neonatal diabetes (71) but familial cases show an autosomal dominant inheritance. Recurrence risk for the offspring of an affected patient is 50%. This is also true for most patients with activating mutations in *ABCC8*. However, some patients are homozygous or compound heterozygous for two different mutations and neonatal diabetes is recessively inherited (49). In this case, the risk of neonatal diabetes for future siblings is 25% but almost inexistent for the offspring. Germline mosaicism (mutations present in the gonads but not detectable in blood) has been reported in several families (71) and hence unaffected parents of a child with an apparently *de novo* mutation should be advised that the recurrence risk in siblings is low but not negligible.

Neonatal diabetes due to mutations in *INS* gene

Heterozygous coding mutations in the *INS* gene are the second most common cause of PNDM after K_{ATP} channel mutations (9, 53, 72, 73). The mutation usually results in a misfolded proinsulin molecule that is trapped and accumulated in the endoplasmic reticulum, leading to endoplasmic reticulum stress and β -cell apoptosis (74).

The severity of intrauterine growth retardation in patients with heterozygous *INS* mutations is similar to that of patients with K_{ATP} channel mutations. In contrast, diabetes presents at a slightly later age although the ranges overlap greatly and patients do not present with neurological features as a direct consequence of the mutation (53).

The majority of heterozygous *INS* mutations are sporadic *de novo* mutations. Only about 20% of probands have a positive family history of autosomal dominant neonatal diabetes (53). Occasionally, *INS* mutations cause permanent diabetes after 6 months of age and therefore genetic testing should be considered in certain situations, especially in patients with antibody-negative type 1 diabetes (12, 73, 75, 76).

In addition to heterozygous *INS* mutations, homozygous or compound heterozygous mutations causing neonatal diabetes have also been described (36). Biallelic mutations do not cause slowly progressive β -cell destruction but result in a lack of insulin biosynthesis before and after birth, which explains much lower birth weights and earlier presentation of diabetes in affected children. As the disease is recessively inherited, there is a 25% recurrence risk in siblings but, in the absence of consanguinity, a very low risk for the offspring of a patient.

Wolcott–Rallison syndrome

Biallelic mutations in *EIF2AK3* (eukaryotic translation initiation factor alpha 2-kinase 3) cause a rare

autosomal recessive syndrome characterized by early-onset diabetes mellitus, spondyloepiphyseal dysplasia, and recurrent hepatic and/or renal dysfunction (77, 78). *EIF2AK3* encodes a protein involved in the regulation of the endoplasmic reticulum stress response. Pancreatic development is rather normal in the absence of the functional protein but misfolded proteins accumulate within the endoplasmic reticulum after birth and eventually induce β -cell apoptosis. Although diabetes usually manifests during infancy, it might not present until 3–4 yr of age. Diabetes may be the first clinical manifestation of the syndrome and therefore this diagnosis needs to be considered in children with PNDM especially if parental consanguinity is present or the patient originates from a highly inbred population (79, 80). As the disease is recessively inherited, there is a 25% recurrence risk in siblings but in the absence of consanguinity, a very low risk for the offspring of a patient.

Neonatal diabetes due to *GCK* mutations

The enzyme glucokinase is considered the glucose sensor of the β cells, as it catalyzes the rate-limiting step of glucose phosphorylation and therefore enables the β cell to respond appropriately to the degree of glycemia (81). Heterozygous mutations in the *GCK* gene produce familial mild non-progressive hyperglycemia (see below). However, complete glucokinase deficiency secondary to mutations in both alleles, either homozygous or compound heterozygous, prevents the β cells from secreting insulin in response to hyperglycemia (82, 83). For this reason, patients present with severe intrauterine growth retardation, are usually diagnosed with diabetes during the first few days of life, and require exogenous insulin therapy. Apart from diabetes, patients do not show any relevant extrapancreatic features.

GCK is responsible for not more than 2–3% of cases of PNDM overall (37). This type of PNDM is inherited in a recessive manner so the recurrence risk for future siblings is 25%. This diagnosis should be strongly considered in probands born to parents with asymptomatic mild hyperglycemia and therefore measuring fasting blood glucose in the parents of any child with neonatal diabetes, even when there is no known consanguinity or family history of diabetes, is often recommended. Sulfonylurea treatment has been tested with no clear effect (P. R. N. and A. T. H., unpublished observations).

IPEX syndrome

Mutations in the *FOXP3* gene are responsible for the IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome (84, 85). This is the only well-established form of PNDM that is associated

with β -cell autoimmunity and pancreatic islet autoantibodies. Among male infants who present with diabetes, immune deficiency, and/or life-threatening infection, mutations in *FOXP3* should be considered. Treatment with immunosuppressive agents (sirolimus or steroids) is recommended (86, 87). Alternatively, allogeneic bone marrow transplantation with reduced-intensity conditioning should be considered (88).

Other causes of neonatal diabetes

The clinical features in other causes of neonatal and infancy-onset diabetes are shown in Table 1. Pancreatic scanning is unreliable in neonates and so it is best to use functional tests of exocrine pancreatic function (fecal elastase and fecal fats) when assessing if pancreatic aplasia is present (89, 90). Apart from K_{ATP} channel neonatal diabetes, all other causes need to be treated with subcutaneous insulin. Patients with pancreatic aplasia/hypoplasia will also require exocrine pancreatic supplements.

Genetic testing should be performed as soon as diabetes is diagnosed in a child aged less than 6 months

Genetic testing will allow diagnosis of a specific type of monogenic diabetes in over 80% of patients whose diabetes is diagnosed before the age of 6 months. As discussed above, this will influence treatment as well as prediction of clinical features. This means that molecular genetic testing is now recommended at the time of diabetes diagnosis in child aged less than 6 months. It is no longer necessary to wait to see if the diabetes resolves or for other features to develop, as major labs will offer comprehensive testing of all NDM subtypes as well as very rapid testing of subtypes that alter treatment.

Autosomal dominant familial mild hyperglycemia or diabetes (MODY)

The different genetic subtypes of MODY differ in age of onset, pattern of hyperglycemia, and response to treatment. Most of them cause isolated diabetes and therefore may be misdiagnosed as either familial type 1 or type 2 diabetes (10, 13, 91). Although the classic criteria for MODY include family history of diabetes, sporadic *de novo* mutations in a number of causative genes have been reported (92).

Three genes are responsible for the majority of MODY cases (*GCK*, *HNF1A*, and *HNF4A*) and will be described in some detail below (see also Table 2). However, up to 13 different genes have been reported to cause autosomal dominant non-insulin dependent diabetes but these are so unusual they do not need to be

Table 2. Common subtypes of MODY and associated clinical features

Gene	Locus	Clinical features	Treatment	References
<i>HNF4A</i>	20q12-q13.1	Macrosomia and neonatal hypoglycemia, renal Fanconi syndrome (mutation specific)	Sulfonylurea	(187)
<i>GCK</i>	7p15-p13	Mild asymptomatic hyperglycemia	Nil/diet	(188)
<i>HNF1A</i>	12q24.2	Renal glucosuria	Sulfonylurea	(189)
<i>HNF1B</i>	17q12	Renal developmental abnormalities, genital tract malformations	Insulin	(190)

MODY, maturity-onset diabetes of the young.

tested for in children with diabetes except in a research setting or when there are additional phenotypes such as pancreatic exocrine dysfunction (93).

Mild fasting hyperglycemia due to glucokinase gene mutations (*GCK*-MODY, MODY2)

The incidental finding of mild hyperglycemia (5.5–8 mmol/L or 100–145 mg/dL) in otherwise asymptomatic children and adolescents raises the possibility that these patients subsequently develop type 1 or type 2 diabetes. In the absence of concomitant pancreatic autoimmunity, the risk of future type 1 diabetes is minimal (94) and a significant proportion will have a heterozygous mutation in *GCK* (95, 96). In peripubertal children and adolescents, the lack of obesity or other signs of insulin resistance should raise concern about a diagnosis of type 2 diabetes.

GCK-MODY is the commonest subtype of monogenic diabetes in the pediatric diabetes clinic and its clinical phenotype is remarkably homogeneous among patients. In contrast to other subtypes of monogenic diabetes, *GCK*-MODY patients regulate insulin secretion adequately but around a slightly higher set point than normal subjects. As a result, they show non-progressive mild hyperglycemia from birth (97). Their hemoglobin A1c (HbA1c) is mildly elevated but usually below 7.5% (98). Despite the mild fasting hyperglycemia, there is usually a small increment in blood glucose during an oral glucose tolerance test (<60 mg/dL or <3.5 mmol/L) (99), although this should not be considered an absolute criterion because of the variability of the oral glucose tolerance test (OGTT). As the degree of hyperglycemia is not high enough to cause osmotic symptoms, most cases are usually diagnosed incidentally when blood glucose is measured for any other reason. Very often, the affected parent remains undiagnosed or has been misdiagnosed with early-onset type 2 diabetes. Measuring fasting glucose in apparently unaffected parents is important when considering a diagnosis of a glucokinase mutation.

As blood glucose does not deteriorate significantly over time, this subtype of monogenic diabetes is rarely

associated with chronic microvascular or macrovascular complications of diabetes (100, 101) and patients do not generally require any treatment (102). Of note, the presence of a *GCK* mutation does not protect against the concurrent development of polygenic type 2 diabetes later in life, which occurs at a similar prevalence than in the general population (103). *GCK*-PNDM may manifest in *GCK*-MODY families since in the setting of consanguinity or a second *de novo* mutation.

Familial diabetes due to *HNF1A*-MODY (MODY3) and *HNF4A*-MODY (MODY1)

The possibility of monogenic diabetes should be considered whenever a parent of a diabetic child has diabetes, even if they are thought to have type 1 or type 2 diabetes. *HNF1A*-MODY is the most common form of monogenic diabetes that results in familial symptomatic diabetes, with heterozygous *HNF1A* mutations being about 10 times more frequent than heterozygous mutations in *HNF4A* (104). Therefore, *HNF1A*-MODY is the first diagnostic possibility to be considered in families with autosomal dominant symptomatic diabetes.

In both *HNF1A*-MODY and *HNF4A*-MODY, glucose intolerance usually becomes evident during adolescence or early adulthood. In the early stages of the disease, fasting blood glucose may be normal but patients tend to show a large increment in blood glucose (>80 mg/dL or 5 mmol/L) after meals or at 2 h during an OGTT (99). Patients with *HNF1A*-MODY demonstrate impaired incretin effect and inappropriate glucagon responses to OGTT (105). Over time, fasting hyperglycemia and osmotic symptoms (polyuria and polydipsia) present but patients rarely develop ketosis because some residual insulin secretion persists for many years. Chronic complications of diabetes are frequent and their development is related to the degree of metabolic control (106). The frequency of microvascular complications (retinopathy, nephropathy, and neuropathy) is similar to that of patients with type 1 and type 2 diabetes. *HNF1A* mutations are associated with an increased frequency of cardiovascular disease (107).

Mutations in *HNF1A* show a high penetrance so that 63% of mutation carriers develop diabetes before 25 yr of age, 79% before age 35 and 96% before 55 yr (6). The age at diagnosis of diabetes is partly determined by the location of the mutation within the gene (108, 109). Patients with mutations affecting the terminal exons (8–10) are diagnosed, on average, 8 yr later than those with mutations in exons 1–6. On the other hand, exposure to maternal diabetes *in utero* (when the mutation is maternally inherited) brings forward the age at onset of diabetes by about 12 yr (99). In the pediatric population, diabetes in *HNF4A* mutation carriers tend to appear at a similar age to patients with mutations in *HNF1A* (16).

There are some differential clinical characteristics between patients with mutations in *HNF4A* and *HNF1A* that can help decide which gene should be considered first in a particular family.

- Patients with *HNF1A* mutations typically have a low renal threshold for glucose reabsorption due to impaired renal tubular transport of glucose and may present postprandial glycosuria before developing significant hyperglycemia (110).
- In addition to diabetes, carriers of the R76W mutation in *HNF4A* present with an atypical form of Fanconi syndrome including hypercalciuria and nephrocalcinosis (111).
- About 50% of *HNF4A* mutation carriers are macrosomic at birth and 15% have diazoxide-responsive neonatal hyperinsulinemic hypoglycemia (112). In this case, hyperinsulinism typically remits during infancy and patients develop diabetes from adolescence (113, 114). Recently, hyperinsulinemic hypoglycemia has also been reported in *HNF1A* mutation carriers (115) but this is very uncommon.

Patients with both *HNF1A*- and *HNF4A*-MODY can initially be treated with diet although they will have marked postprandial hyperglycemia with high carbohydrate food (99). Most patients will need pharmacological treatment as they show progressive deterioration in glycemic control. They are extremely sensitive to sulfonylureas (116), which usually allow a better glycemic control than that achieved on insulin, especially in children and young adults (117). The initial dose should be low (one-quarter of the normal starting dose in adults) to avoid hypoglycemia. As long as the patients do not have problems with hypoglycemia, they can be maintained on low-dose sulfonylureas (e.g., 20–40 mg gliclazide daily) for decades (118, 119). If there is hypoglycemia despite dose titration of a once or twice daily sulfonylurea preparation, a slow release preparation or meal time doses with a short-acting agent such as nateglinide may be considered (120, 121). A recent randomized controlled trial

comparing a glucagon-like peptide (GLP-1) agonist with a sulfonylurea demonstrated lower fasting glucose in those treated with the GLP-1 agonist (122).

Genetic syndromes associated with diabetes

A monogenic disorder should be considered in any child with diabetes associated with multi-system extrapancreatic features (123). These syndromes may either cause neonatal diabetes (Table 1) or present later in life (see below). The online Mendelian inheritance in Man website (www.ncbi.nlm.nih.gov/omim or www.omim.org) can help with clinical features and to know if the gene for a particular syndrome has been defined and hence molecular genetic testing is available. Genetic testing for some of these conditions is available on a research basis at www.euro-wabb.org (124). The most common syndromes usually presenting beyond infancy are described in some detail below.

Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness syndrome (Wolfram syndrome)

The association of diabetes with progressive optic atrophy below 16 yr of age is diagnostic of this autosomal recessive syndrome (125). Non-autoimmune insulin-deficient diabetes is usually the first manifestation of the disease and presents at a mean age of 6 yr, although may present anytime from early-infancy (126, 127). Patients require insulin treatment from diagnosis. Other typical clinical features, such as sensorineural deafness, central diabetes insipidus, urinary tract dilatations, and neurological symptoms develop later in a variable order even within the same family. Many patients with Wolfram Syndrome (WFS) are initially diagnosed as having type 1 diabetes; subsequent loss of vision, which occurs approximately 4 yr after diabetes diagnosis, may be misdiagnosed as diabetic retinopathy (128, 129). Patients WFS die at a median age of 30 yr, mainly from neurodegenerative complications.

At least 90% of patients harbor recessively acting mutations in the *WFS1* gene (130, 131). A second variant of the syndrome has recently been described in association with mutations in *CISD2* (132). Patients with this rare variant do not develop diabetes insipidus but present with additional symptoms including bleeding diathesis and peptic ulcer disease.

Renal cysts and diabetes syndrome (*HNF1B*-MODY or MODY5)

Although initially described as a rare subtype of familial diabetes, it is now clear that patients with heterozygous mutations in *HNF1B* rarely present with isolated diabetes (133). In contrast, renal developmental disorders (especially renal cysts and renal dysplasia) are present in almost all patients

with *HNF1B* mutations or gene deletions (8) and constitute the main presentation in children, even in the absence of diabetes (134). Genital-tract malformations (particularly uterine abnormalities), hyperuricemia and gout can also occur, as well as abnormal liver function tests (133). Diabetes develops later, typically during adolescence or early adulthood (135, 136), although transient neonatal diabetes has been reported in a few cases (35, 137). In addition to insulin deficiency related to pancreatic hypoplasia (138), patients also show some degree of hepatic insulin resistance (139), which explains why they do not respond adequately to sulfonylurea treatment and require early insulin therapy (6). Moreover, mutation carriers have lower exocrine pancreatic function with reduced fecal elastase; this involves both ductal and acinar cells (140). Therefore, the phenotype of renal cysts and diabetes (RCAD) patients is highly variable even within families sharing the same *HNF1B* mutation and therefore this diagnosis should be considered not only in the diabetes clinic but also in other clinics (nephrology, urology, gynecology, etc.). In patients found to have renal cysts, imaging of the pancreas is indicated, as the absence of the pancreatic body and/or tail is highly indicative of *HNF1B*-MODY (141). Fecal elastase should also be measured, as this is always abnormal in patients with *HNF1B*-MODY (140). Importantly, a family history of renal disease or diabetes is not essential to prompt genetic testing, as spontaneous mutations and deletions of this gene are common (one third to two thirds of cases) (8, 134).

Mitochondrial diabetes

Diabetes due to mitochondrial mutations and deletions is rarely seen in the pediatric age group as the vast majority of patients develop diabetes as young or middle-aged adults. The most common form of mitochondrial diabetes is caused by the m.3243A>G mutation in mitochondrial DNA. Diabetes onset is usually insidious but approximately 20% of patients have an acute presentation, even in diabetic ketoacidosis (142). Although it typically presents in adulthood, some cases have been reported in adolescents with a high degree of heteroplasmy (143, 144). Mitochondrial diabetes should be suspected in patients presenting with diabetes and sensorineural hearing loss inherited from mother's side. Interestingly, the same m.3243A>G mutation also causes a much more severe clinical syndrome known as MELAS (myopathy, encephalopathy, lactic acidosis, and stroke) (145).

Patients with mitochondrial diabetes may respond initially to diet or oral hypoglycemic agents but often require insulin treatment within months or years. Metformin should be avoided as it interferes with

mitochondrial function and may trigger episodes of lactic acidosis (146).

The penetrance of diabetes in mutation carriers depends on the age considered, but is estimated to be above 85% at 70 yr (142). Affected males do not transmit the disease to their offspring. In contrast, females transmit the mutation to all their children, although some may not develop the disease (6). In addition to the m.3243A>G mutation, early-onset diabetes (even in infancy) has been reported in other less common mitochondrial disorders such as Kearns–Sayre syndrome (147) and Pearson syndrome (148).

Diabetes secondary to monogenic diseases of the exocrine pancreas

Heterozygous mutations in *CEL*, which encodes a pancreatic lipase, cause an autosomal dominant disorder of pancreatic exocrine insufficiency and diabetes (93). Importantly, the exocrine component of the syndrome is initiated already in childhood, 10–30 yr before diabetes develops, and can be revealed by lowered fecal elastase and/or pancreatic lipomatosis (149, 150). Other autosomal dominant monogenic diseases affecting mainly the exocrine pancreas that can lead to diabetes sooner or later include cystic fibrosis (*CFTR*) (151), hereditary pancreatitis (*PRSS1* and *SPINK1*) (152), and pancreatic agenesis/hypoplasia (*GATA6*) (90).

Monogenic insulin resistance syndromes

The key features of insulin resistance syndromes are moderate to severe acanthosis nigricans associated with either severely increased insulin concentrations or increased insulin requirements (depending on whether the patient has diabetes already), usually in the absence of a corresponding degree of obesity. Three different groups have been proposed based on the pathogenesis of the disease: primary insulin signaling defects, insulin resistance secondary to adipose tissue abnormalities, and insulin resistance as a feature of complex syndromes (153). Clinical and biochemical characterization of patients with severe insulin resistance may be used to guide genetic testing, as it happens with monogenic β -cell diabetes (Table 3). However, diabetes associated with monogenic severe insulin resistance is far less common than monogenic β -cell failure, especially in prepubertal children as hyperglycemia is usually a late event in the natural history of these disorders (154). As ovarian hyperandrogenism usually is the commonest presentation in adolescents, there is a gender bias in the diagnosis. The most relevant disorders are briefly described below.

Table 3. Classification of syndromes of severe insulin resistance (modified from reference 154)

Insulin resistance syndrome subtype		Gene (inheritance)	Leptin	Adiponectin	Other clinical features
Primary insulin signaling defects Adipose tissue abnormalities	Receptor defect	<i>INSR</i> (AR or AD)	Decreased	Normal or elevated	No dyslipidemia No fatty liver
	Post receptor defects	<i>AKT2</i> , <i>TBC1D4</i> (AD)	Increased (low in <i>LEP</i>)		Tall stature (<i>MC4R</i>) Hypogonadism (<i>LEP</i>) Hypoadrenalism (<i>POMC</i>)
	Monogenic obesity	<i>MC4R</i> (AD) <i>LEP</i> , <i>LEPR</i> , <i>POMC</i> (AR) Others			Severe dyslipidemia (high triglycerides, low HDL cholesterol) Fatty liver
	Congenital generalized lipodystrophy	<i>AGPAT2</i> , <i>BSCL2</i> (AR) Others	Decreased	Decreased	Myopathy and cardiomyopathy (<i>LMNA</i>) Pseudoacromegaly (<i>PPARG</i>) SHORT syndrome with partial lipodystrophy, insulin resistance and diabetes (<i>PIK3R1</i>)
Partial lipodystrophy	<i>LMNA</i> , <i>PPARG</i> , <i>PIK3R1</i> (AD) Others	Variable			
Complex syndromes	Alström	<i>ALMS1</i> (AR)			
	Bardet–Biedl	<i>BBS1</i> to <i>BBS18</i> (mostly AR)			
	DNA damage repair disorders	<i>WRN</i> (AR) <i>BLM</i> (AR)			
	Primordial dwarfism	<i>PCNT</i> (AR)			

AD, autosomal dominant; AR, autosomal recessive; HDL, high-density lipoprotein; SHORT, short stature, hypermobility of joints, ocular depression, Rieger's anomaly, and teething delay syndrome.

Primary insulin signaling defects due to mutations in the insulin receptor gene

Insulin receptor (*INSR*) gene mutations are responsible for a number of rare insulin resistance syndromes (155). Leptin levels are low, but adiponectin levels are normal or elevated as insulin normally inhibits adiponectin secretion. The most common form is type A insulin resistance syndrome, which is usually diagnosed in non-obese female adolescents with severe acanthosis nigricans and hyperandrogenism (polycystic ovarian syndrome) and may show autosomal dominant or autosomal recessive inheritance. Mutations in both alleles of *INSR* are also responsible for the more severe Donohue syndrome (formerly known as Leprechaunism) and Rabson–Mendenhall syndrome. The presenting complaint is failure to thrive, with impaired linear growth and weight gain, associated to overgrowth of soft tissues. Postprandial hyperglycemia may be severe but is usually accompanied by fasting hypoglycemia.

Metabolic control in patients with *INSR* mutations remains poor and long-term diabetes complications are frequent. Insulin sensitizers may be tried initially but most patients need extraordinarily high doses of insulin, with limited effect (155). As an alternative therapeutic method for young children, recombinant human insulin-like growth factor (IGF-I) has been reported to improve both fasting and postprandial glycemia although long-term effects on survival remain unclear (156).

Monogenic lipodystrophies

Lipodystrophies are characterized by a selective lack of adipose tissue, which results in decreased adipokines

levels and insulin resistance (157). Mutations in either *AGPAT2* or *BSCL* account for approximately 80% of cases of congenital generalized lipodystrophy (Berardinelli–Seip syndrome) (158). This is a recessive disorder characterized by an almost complete absence of subcutaneous and visceral fat with abdominal distention due hepatic steatosis, which may evolve to hepatic fibrosis. Diabetes usually becomes apparent in early adolescence. In contrast, familial partial lipodystrophy is usually recognized after puberty in patients with loss of subcutaneous fat from the extremities and lower trunk and progressive accumulation of subcutaneous adipose tissue in the face and around the neck. Visceral fat is greatly increased. In addition to hyperinsulinemia, hypertriglyceridemia, and decreased high-density lipoprotein (HDL) cholesterol, patients also show signs of hyperandrogenism and sometimes pseudoacromegalic growth of soft tissues. Diabetes usually appears in late adolescence or early adulthood. Heterozygous mutations in *LMNA* or *PPARG* account for approximately 50% of cases (157). Two recent causes of lipodystrophy and multi-system disease are: (i) subcutaneous lipodystrophy and diabetes, deafness, mandibular hypoplasia, and hypogonadism in males associated with a specific mutation in *POLD1*, a universal DNA polymerase (159) and (ii) SHORT (short stature, hypermobility of joints, ocular depression, Rieger's anomaly, and teething delay) syndrome with partial lipodystrophy, in which IR and diabetes were caused by a hot spot mutation in *PIK3R1* encoding p85 that has a central role in the insulin-signaling pathway (160).

Dietary advice with a low-fat, sometimes hypocaloric diet is the mainstay of treating lipodystrophies as it can have a dramatic effect on metabolic derangements.

In partial lipodystrophy, insulin sensitizers such as metformin and glitazones may be initially effective (161) but glitazones can cause further accumulation of fat in the face and neck (154). Patients with severe congenital lipodystrophy greatly benefit from treatment with recombinant leptin (162). In partial lipodystrophy, leptin replacement has limited value with improvement of hypertriglyceridemia but not hyperglycemia (163).

Ciliopathy-related insulin resistance and diabetes

Alström syndrome (ALMS). This autosomal recessive disorder shares symptoms with Bardet–Biedl syndrome (BBS) (see below), including progressive visual impairment related to cone–rod dystrophy, sensorineural hearing loss, obesity, and diabetes mellitus. It can be distinguished from the latter syndrome by the lack of polydactyly and hypogonadism and by the absence of cognitive impairment (164). More than 60% of individuals with ALMS develop cardiomyopathy. The syndrome is caused by mutations within the *ALMS1* gene of unknown function (165). Patients ALMS usually show many features of the metabolic syndrome including acanthosis nigricans, hyperlipidemia, hyperuricemia, hypertension, and slowly progressive insulin-resistant diabetes (166). Lifestyle intervention can initially ameliorate the metabolic abnormalities (167).

Bardet–Biedl syndrome. This disorder is characterized by intellectual disability, progressive visual impairment due to cone–rod dystrophy, polydactyly, obesity, diabetes mellitus, renal dysplasia, hepatic fibrosis, and hypogonadism. Obesity is found in almost every patient, while diabetes affects less than 50% (168). While the syndrome shares some similarities with Lawrence–Moon syndrome, these two disorders can be distinguished by the presence of paraplegia and the absence of polydactyly, obesity, and diabetes mellitus in Lawrence–Moon syndrome. Terms such as Lawrence–Moon–Bardet–Biedl or Lawrence–Moon–Biedl syndrome should therefore be avoided. BBS has been linked to 18 different genetic loci, referred to as *BBS1* to *BBS18* (169, 170). The majority of cases are autosomal recessive (171), but triallelic inheritance has been reported (172). Genetic diagnostic laboratories and detailed clinical recommendations for patients with ALMS and BBS are present at <http://www.euro-wabb.org>.

Conclusions

Advances in molecular genetics have led to the identification of genes associated with many clinically identified subgroups of diabetes. Molecular genetic

testing is being used as a diagnostic tool that can help define the diagnosis and treatment of children with diabetes. As these tests are expensive, diagnostic genetic testing should be limited to those patients who are likely to harbor a mutation on clinical grounds.

Conflicts of interest

The authors have declared no conflicts of interest.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Management of cystic fibrosis-related diabetes in children and adolescents

Moran A, Pillay K, Becker DJ, Acerini CL.
Management of cystic fibrosis-related diabetes in children and adolescents.
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Executive summary and Recommendations

- Cystic fibrosis-related diabetes (CFRD) is the most common co-morbidity associated with cystic fibrosis (CF).
- The pathophysiology of CFRD is complex and includes the loss of pancreatic islet cells leading to both insulin and glucagon deficiency, fluctuating insulin resistance, the requirement for high caloric intake, gut abnormalities including delayed gastric emptying, altered intestinal motility, and liver disease.
- CFRD can occur at any age, including infancy, and its prevalence increases as patients get older.
- Few individuals with CF have normal glucose tolerance and even when the fasting and 2-h oral glucose tolerance test (OGTT) glucose levels are normal, variable, intermittent post-prandial hyperglycemia can often be detected by continuous glucose monitoring (CGM).
- CF is associated with a progressive deterioration in glucose tolerance as individuals grow older, including indeterminate glycemia followed by impaired glucose tolerance (IGT) and finally diabetes.
- Early CFRD is characterized by normal fasting glucose levels, but over time fasting hyperglycemia develops. At any particular time blood glucose levels can vary, dependent upon acute changes in pulmonary and infectious status.
- The majority of patients have no obvious symptoms at diagnosis, although symptoms may develop insidiously. Presentation with CFRD is more likely during times when insulin resistance is increased (e.g. pulmonary infection, use of glucocorticoid agents).
- Presentation with Diabetic ketoacidosis (DKA) is rare.
- The onset of CFRD is defined as the date a person with CF first meets diabetes diagnostic criteria, even if hyperglycemia subsequently abates. [E, Consensus]
- During a period of stable baseline health the diagnosis of CFRD can be made in CF patients according to standard American Diabetes Association (ADA) criteria. [E, Consensus]
- The diagnosis of CFRD can be made in CF patients with acute illness when fasting plasma glucose (FPG) levels ≥ 126 mg/dL (7.0 mmol/L) or 2-h post-prandial

- plasma glucose levels ≥ 200 mg/dL (11.1 mmol/L) persist for more than 48 h. [E, Consensus]
- CF patients with gestational diabetes are not considered to have CFRD, but require CFRD screening 6–12 wk after the end of the pregnancy. [E, Consensus]
 - Distinguishing between CFRD with and without fasting hyperglycemia is not necessary. [B]
 - The use of hemoglobin A1c (HbA1c) as a screening test for CFRD is not recommended. [B]
 - Screening for CFRD should be performed using the 2-h 75 g (1.75 g/kg) OGTT. [E, Consensus]
 - Annual screening for CFRD should begin by age 10 yr in all CF patients who do not have CFRD. [B]
 - Patients with CFRD should ideally be seen quarterly by a specialized multidisciplinary team with expertise in diabetes and CF. [E, Consensus]
 - Patients with CFRD should receive ongoing diabetes self-management education from diabetes education programs that meet national standards. [E, Consensus]
 - CF patients with CFRD should be treated with insulin therapy. [A]
 - Oral diabetes agents are not as effective as insulin in improving nutritional and metabolic outcomes in CFRD, and are not recommended outside the context of clinical research trials. [A]
 - Patients with CFRD who are on insulin should perform self-monitoring of blood glucose at least three times a day. [E, Consensus]
 - Patients with CFRD should strive to attain plasma glucose goals as per the ADA recommendations for all people with diabetes, bearing in mind that higher or lower goals may be indicated for some patients, and that individualization is important. [E, Consensus]
 - HbA1c measurement is recommended quarterly for patients with CFRD to guide insulin therapy decisions. [E, Consensus]
 - CF Foundation evidence-based guidelines for nutritional management of all persons with CF are recommended for patients with CFRD. [E, Consensus]
 - Education about the symptoms, prevention, and treatment of hypoglycemia, including the use of glucagon, is recommended for patients with CFRD and their care partners. [E, Consensus]
 - Annual monitoring for microvascular complications of diabetes is recommended, beginning 5 yr after the diagnosis of CFRD or, if the exact time of diagnosis is not known, at the time that fasting hyperglycemia is first diagnosed. [E, Consensus]
 - Patients with CFRD diagnosed with hypertension or microvascular complications should receive usual treatment, except that there is no restriction of

sodium and, in general, no protein restriction. [E, Consensus]

- An annual lipid profile is recommended for patients with CFRD and pancreatic exocrine sufficiency [E, Consensus]

Cystic fibrosis (CF) is the most common lethal genetic autosomal recessive disease in Caucasians, with a worldwide prevalence of 1 in 2500 live births. Cystic fibrosis-related diabetes (CFRD) is the most common co-morbidity in CF. There are important pathophysiologic differences between CFRD and type 1 and type 2 diabetes (Table 1); which necessitate a unique approach to diagnosis and management. Factors specific to CF which impact glucose metabolism include the loss of total islets leading to both insulin and glucagon deficiency, chronic and acute inflammation and infection which cause fluctuating insulin resistance, a requirement for high caloric intake because of increased energy expenditure and malabsorption, risk of life-threatening malnutrition, and gut abnormalities including delayed gastric emptying, altered intestinal motility, and liver disease.

Diagnostic criteria for CFRD and abnormal glucose tolerance

The diagnostic criteria for CFRD were updated in 2010 in North America by the CFRD Guidelines Committee, in a position statement co-sponsored by the American Diabetes Association (ADA) and the Cystic Fibrosis Foundation, and endorsed by the Pediatric Endocrine Society (1). They are identical to those used to diagnose other forms of diabetes, including the relatively recent addition of hemoglobin A1c (HbA1c) as a diagnostic criterion. It should be noted, however, that low or normal HbA1c levels do not exclude the diagnosis of CFRD because HbA1c is often spuriously low in CF.

CFRD is part of a spectrum of progressive glucose tolerance abnormalities defined by a standard oral glucose tolerance test (OGTT) (Table 2). Few individuals with CF have truly normal glucose tolerance (NGT). Even when the fasting and 2-h OGTT glucose levels normal, variable, intermittent post-prandial hyperglycemia can often be detected at home by continuous glucose monitoring (CGM) (2, 3). With time, as glucose tolerance worsens, indeterminate glycemia develops (INDET, mid-OGTT glucose ≥ 11.1 mmol/L), followed by impaired glucose tolerance (IGT) and finally diabetes. The early stage of diabetes is characterized by normal fasting glucose levels, but over time fasting hyperglycemia develops. Isolated impaired fasting glucose (IFG) is sometimes present in persons with CF (4, 5).

There is a general pattern of progressive deterioration of glucose tolerance as individuals with CF grow

Table 1. Comparison of features of different forms of diabetes

	Type 1	Type 2	CFRD
Prevalence	0.2%	11%	35%
Onset	Usually acute	Insidious	Insidious
Peak age of onset	Children, Youth	Adults	18–24 yr
Usual body habitus	Normal	Obese	Normal–Underweight
Autoimmune etiology?	Yes	No	No
Insulin deficiency	Nearly complete	Partial, Variable	Severe, Not complete
Insulin sensitivity	Somewhat decreased	Severely decreased	Somewhat decreased*
Ketones	Yes	Rare	Rare
Usual treatment	Insulin	Diet, Oral Meds, Insulin	Insulin
Microvascular complications	Yes	Yes	Yes
Macrovascular complications	Yes	Yes	No
Metabolic syndrome	No	Yes	No
Cause of death	Cardiovascular	Cardiovascular	Pulmonary

CFRD, cystic fibrosis-related diabetes.

*Insulin sensitivity becomes severely decreased during acute illness.

Table 2. Abnormal glucose tolerance categories in CF

Category	FPG (mmol/L)	2-h glucose (mmol/L)	Notes
Normal (NGT)	<7.0	<7.8	All glucose levels <11.1
Indeterminate (INDET)	<7.0	<7.8	Mid-OGTT glucose ≥11.1
Impaired (IGT)	<7.0	7.8–11.1	
CFRD FH–	<7.0	≥11.1	
CFRD FH+	≥7.0		

FPG = fasting plasma glucose; FH = fasting hyperglycemia; CFRD, cystic fibrosis-related diabetes; OGTT, oral glucose tolerance test.

older. However, at any particular time glucose levels can vary, dependent upon acute changes in pulmonary and infectious status. The CFRD Guidelines Committee defined the onset of CFRD as the first time a patient meets diagnostic criteria for diabetes, even if glucose tolerance subsequently appears to improve, because long-term outcomes in microvascular disease and mortality correlate with a duration of diabetes that includes these early years when diabetes appears to wax and wane, and because once a patient has experienced significant hyperglycemia, even in the context of acute illness, it generally recurs (1). Hyperglycemia is common during pregnancy in women with CF because of their underlying insulin insufficiency (6, 7); women with CF who have gestational diabetes and who do not meet diagnostic criteria for diabetes before or after pregnancy are not considered to have CFRD.

Incidence and prevalence

The incidence and prevalence of diabetes in persons with CF is higher than in any other age-matched group. An age-dependent incidence of 4–9% per year was

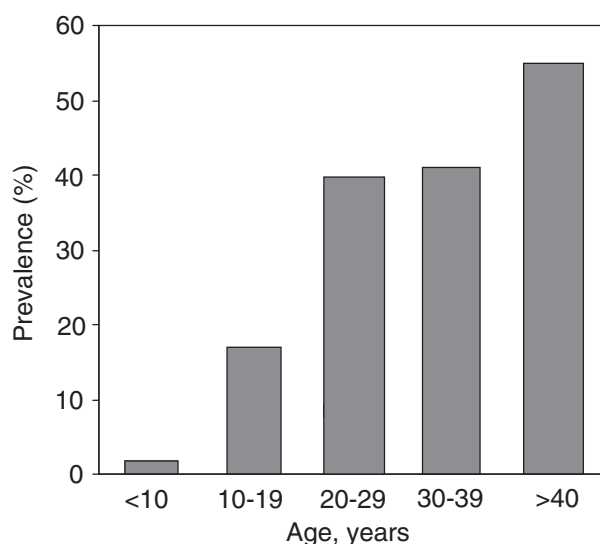


Fig. 1. Prevalence of CFRD by age group at the University of Minnesota, in a population of more than 500 patients (9).

reported in the 1990s in Denmark (8). The University of Minnesota has reported an incidence of 2.7 cases per 100 patient years (9). The reported prevalence of CFRD may be underestimated at centers which do not do universal OGTT screening.

CFRD can occur at any age including infancy. However, prevalence increases as patients get older. The European Epidemiologic Registry of Cystic Fibrosis (ERCF) reported 5 and 13% prevalence in age groups 10–14 and 15–19 yr, respectively (10). A prospective trial from Ireland reported similar prevalence figures: NGT-69%, IGT-14%, and CFRD-17% in the 10–19 yr age group (11). In Denmark, 50% of patients developed CFRD by 30 yr of age (12). At one US center, diabetes was found in <5% of children aged 10 yr and younger, 15–20% of adolescents, ~40% of those in their 20s and 30s, and >50% of those older than 40 yr (9) (Figure 1).

Pathophysiology of CFRD

The pathophysiology of CFRD is complex. The primary defect, insulin insufficiency, is present in essentially all CF patients, and is related to collateral damage to the islets as exocrine tissue is destroyed. Not all CF patients develop diabetes, however, and metabolic outcome is influenced by other factors including the severity of inflammation and infection, genetic susceptibility, malnutrition, and perhaps the CF chloride channel defect itself.

Pancreatic pathology

Abnormal chloride channel function results in thick viscous secretions and obstructive damage to the exocrine pancreas with progressive fibrosis and fatty infiltration. This results in disruption and destruction of islet architecture leading to loss of endocrine beta, alpha, and pancreatic polypeptide cells (13–15). Most CF patients, with or without diabetes, have lost about half of their islet mass. Beta-cell destruction is not related to autoimmune disease in CF, since the frequency of diabetes autoantibodies and human leukocyte antigen (HLA) types associated with type 1 diabetes are similar to that of the general population (16, 17). However, individuals have occasionally been found to have both type 1 diabetes and CF.

The role of insulin insufficiency

The primary defect in CFRD is severe but not absolute insulin insufficiency. Virtually all exocrine insufficient patients with CF, with and without diabetes, show evidence of beta-cell dysfunction (8, 18). Fasting insulin and C-peptide concentrations are initially normal, but there is delay and blunting of peak insulin secretion during a standard OGTT (19). This effect is more pronounced with worsening glycemic status (20–22). Delayed insulin secretion during the OGTT is related to loss of first phase insulin secretion, which is found even in CF patients with normal glucose tolerance (23). Glucagon secretion is also impaired in CF because total islets are destroyed (19, 23).

The role of insulin resistance

In CF patients *without* diabetes, insulin sensitivity has generally been reported to be intact, although some investigators have found insulin resistance which is likely related to more severe illness (24–28). While most of these patients are sensitive to insulin when they are in their baseline state of health, insulin resistance is acutely increased during periods of active infection. CF patients *with* diabetes are modestly insulin resistant, with both decreased peripheral glucose uptake and

poor insulin suppression of hepatic glucose production (26, 27). Insulin resistance is not as important as insulin insufficiency in the pathogenesis of CFRD, but it assumes a greater role during periods of stress such as acute pulmonary disease from infectious exacerbations.

Genetics of CFRD

CF is caused by a mutation in the CF transmembrane conductance regulator (CFTR), a chloride channel. Diabetes mainly occurs in people with CFTR mutations which produce severe disease including exocrine pancreatic insufficiency. CFTR is expressed in the beta cell (29, 30), where its role is unknown. The ferret model of CF demonstrates abnormal insulin secretion from birth, suggesting that CFTR might play an intrinsic role in insulin secretion (31). This notion is supported by a small human pilot study in CF patients who demonstrated an improved insulin response to oral and intravenous glucose after receiving a new CFTR corrector agent (32).

A genetic association between CF and type 2 diabetes is suggested by the increased prevalence of type 2 diabetes in monozygotic vs. dizygotic twins with CF (33), an increased prevalence of CFRD in individuals with a family history of type 2 diabetes (34), and an association with type 2 diabetes susceptibility loci (34, 35). There is also a relation between CFRD and genes associated with inflammation such as tumor necrosis factor (36), heat shock protein (37), and calpain 10 (38). These findings have led to the hypothesis that while the primary pathologic defect in CFRD is partial loss of islets due to physical destruction, those subjects with underlying defects in insulin secretion or sensitivity may be more susceptible to diabetes because they are less able to compensate for reduced beta-cell mass.

Clinical features of CFRD

CFRD develops insidiously. Symptoms of CFRD are listed in Table 3. It is important to note, however, that the majority of patients have no obvious symptoms. Diabetic ketoacidosis (DKA) is rare, most likely because of the persistence of endogenous insulin

Table 3. Symptoms of CFRD

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- Unexplained polyuria or polydipsia
 - Failure to gain or maintain weight despite nutritional intervention
 - Poor growth velocity
 - Delayed progression of puberty
 - Unexplained chronic decline in pulmonary function
 - There may be no symptoms
-

CFRD, cystic fibrosis-related diabetes.

secretion or because glucagon secretion is also impaired. CFRD may first present during situations where insulin resistance is increased, such as acute pulmonary infection or glucocorticoid therapy, or during high-carbohydrate food supplementation such as continuous nighttime drip feedings. Diabetes is common in the setting of lung transplantation, where pre-transplant patients are critically ill and thus quite insulin resistant, and where post-transplant patients receive diabetogenic medications such as steroids and calcineurin inhibitors (39–42). The prevalence of CFRD is higher in patients with liver disease (43).

Survival and prognosis

Increased mortality in CFRD

Beginning in the 1980s, several investigators in the USA and Europe documented that the additional diagnosis of diabetes was associated with increased mortality in CF, and that women with CFRD were at particularly high risk for early death (44–48). Those with CFRD, like all CF patients, almost always die from pulmonary failure rather than from the macrovascular and microvascular disease associated with death in persons with type 1 and type 2 diabetes. Diabetes has been directly implicated in the pathophysiology of CF lung function decline because of both the catabolic effect of insulin insufficiency on nutritional status and muscle mass (49–52) and the negative impact of chronic hyperglycemia on lung function (53–56), the latter of which may be mediated at least in part by permitting a pro-inflammatory, bacteria-permissive environment.

A 2009 report examined temporal trends in CFRD mortality in a large well-defined CF population that had been followed longitudinally at one institution since the early 1990s (9). Between 1992 and 2008, there was a significant and steady decline in the risk of death associated with CFRD. In the early 1990s, mortality was 13.4-fold greater in individuals with CFRD compared to those without diabetes; by 2008 this had dropped to a 3.5-fold difference which was only significant in patients older than 30 years, and the gender difference in mortality had disappeared. This substantial improvement in the mortality associated with CFRD was attributed to annual diabetes screening and early institution of insulin therapy.

Microvascular and macrovascular complications

Diabetes microvascular complications occur in CFRD, but they tend to be relatively mild in nature (although there are case reports of patients with more severe disease). In Denmark, 36% of patients with more than 10 yr duration of diabetes had retinopathy (57). In a US series of 285 CFRD patients, diabetes complications

were rare before 10 yr duration of diabetes, after which time, in subjects with fasting hyperglycemia, microalbuminuria was found in 14%, retinopathy 16%, neuropathy 55%, and gastropathy 50% of subjects (58). No microvascular complications were found in CFRD patients who had never experienced fasting hyperglycemia (1).

Death from macrovascular complications has not been reported in CF. This is important because the risk of macrovascular disease has shaped treatment and therapy recommendations for persons with type 1 and type 2 diabetes; many of these recommendations are not relevant in CF and may even be harmful. Cholesterol levels are generally low in CF, but isolated triglyceride elevation is not uncommon (59–63). Lipid elevation may be more common after lung transplantation and in older patients with less severe CF mutations. The clinical significance of abnormal lipid levels is unknown but may assume more relevance as the CF population ages.

Hypoglycemia

Hypoglycemia is relatively common in persons with CF with or without diabetes. Fasting hypoglycemia was found in 14% of 129 children and adults with CF at an Italian center and was related to poor clinical status (worse lung function, increased hospitalizations) (28). In this same cohort, reactive hypoglycemia was found during 15% of OGTTs, whereas in a German study 6.3% of patients had reactive hypoglycemia following their OGTT (64). This is presumed to be related to delayed insulin secretion. Although CF patients have diminished glucagon secretion, they have normal recovery from insulin-induced hypoglycemia, likely because of an intact catecholamine response (23). As with all patients on insulin therapy, hypoglycemia is a risk that patients and their families must know how to anticipate, prevent, and treat.

Increased morbidity in the pre-diabetes state

Several studies have shown an insidious decline in clinical status in the years before the diagnosis of CFRD, in the insulin insufficient, pre-diabetic state (44, 65–68). In a prospective study, the decline in pulmonary function over 4 yr was least in patients with NGT, greater in patients with IGT, and greatest in CF patients with untreated early (without fasting hyperglycemia) diabetes (66). In this study and others (28), pulmonary deterioration correlated with the severity of insulin insufficiency. Because of the association between protein catabolism, malnutrition and death in CF and the potent anabolic effect of insulin, the nutritional impact of insulin insufficiency appears to be of greater consequence in CF than the

metabolic impact of hyperglycemia. This may result in clinical compromise long before glucose levels are high enough to qualify for a diagnosis of diabetes. The catabolic effect of insulin insufficiency may be most important in growing children (69–71).

Screening for CFRD

Because CFRD is often clinically silent, routine screening is important. The standard OGTT (patient fasted for 8 h, 1.75 g/kg body weight oral glucose up to a maximum of 75 g, 2-h test) is at present the only accepted screening test.

Oral glucose tolerance testing (OGTT)

The North American CFRD Guidelines Committee determined that the OGTT is the screening test of choice for CFRD (1), based on the poor performance of other tests in CF, the availability of long-term prognostic data linking OGTT results to relevant clinical outcomes, and the importance of diagnosing diabetes early in its course when fasting glucose levels are still normal. Nearly two thirds of patients with CFRD do not have fasting hyperglycemia (9), and this condition can only be detected by OGTT. It is important to identify these individuals because they are at high risk for significant lung function decline and for progression to fasting hyperglycemia (8), and because insulin therapy has been shown to improve nutritional status in this population (72). The OGTT also identifies individuals with abnormal glucose tolerance. In a large study of more than 1000 German and Austrian CF patients, IFG, IGT, and indeterminate glycemia were all predictors of future CFRD (73).

During pregnancy, diabetes poses a risk for both the mother and fetus. Gestational diabetes develops early in pregnancy in CF (6, 7, 74). OGTT screening for pre-existing diabetes should be done before or immediately after the onset of pregnancy, and screening for gestational diabetes is recommended at the end of both the first and second trimesters (1).

There is emerging evidence that mid-OGTT glucose levels may be even more predictive of clinical decline than the 2-h level, and thus consideration should be given to measuring glucose levels every half an hour during the 2-h test (55, 73, 75, 76). It is recommended that OGTT screening begin by at least 10 yr of age. While diabetes *per se* is rare before age 10, 42–78% of children aged 9 and below are reported to have abnormal glucose tolerance (7, 77, 78). A prospective longitudinal study at one North American CF center found that in children aged 6–9, IGT or indeterminate glycemia each predicted a high risk of progression to diabetes in the early adolescent years (78). For this

reason, some centers chose to begin screening at the age of 6.

HbA1c as a diagnostic tool

HbA1c has been shown by several investigators to be unreliable in the diagnosis of CFRD because it is spuriously low (8, 44, 79). This has been postulated to be due to increased red blood cell turnover related to inflammation. In one study, only 16% of patients with CFRD had an elevated HbA1c at the time of diagnosis (8). An elevated HbA1c is evidence of hyperglycemia, but a normal HbA1c does not exclude it.

Random and fasting glucose levels, SMBG for CFRD diagnosis

Normal fasting or random glucose levels do not exclude a diagnosis of diabetes in CF. In some high-risk situations such as home intravenous antibiotic or glucocorticoid therapy or nighttime gastrostomy feedings, it is practical to have the patient perform initial pre-screening at home by self-monitoring of blood glucose (SMBG). SMBG is not sufficiently accurate to make a diagnosis of diabetes, and subsequent laboratory screening by the methods listed below under ‘Recommendations’ must occur in patients identified as high risk by SMBG.

Continuous glucose monitoring (CGM)

CGM has been validated and proven to be useful in children and adolescents with CFRD, where it can help guide safe and effective insulin therapy (2). Its role in CF patients who do not have diabetes is less clear. CGM is not accurate enough to be used to make a diagnosis of diabetes. Furthermore, while it is well known that post-prandial glycemic abnormalities that can be detected by CGM exist in patients with CF long before OGTT results move from NGT to IGT or diabetes, to date the clinical significance of these brief elevations in glucose excursion remains unknown (75, 80).

Treatment of CFRD

Medical nutritional therapy

The dietary recommendations for persons with CFRD are very different from those for persons with type 1 and type 2 diabetes (Table 4), both because their needs are very different, and because they are at low risk for cardiovascular disease. All CF patients, including those with diabetes, require a high calorie, high salt, high fat diet. Caloric restriction is almost never appropriate (although it may be considered in older patients

Table 4. Dietary recommendations for CFRD

	Types 1 and 2 diabetes	CFRD
Calories	≤100% of normal for age and gender – often have to watch or restrict calories to prevent overweight	Usually require 120–150% (or more) of normal caloric intake for age and gender to prevent underweight
Fat	<35% of total energy	40% of total energy
Total carbohydrate	45–60% total energy	45–50% of total energy
Fiber	~3.3 g of fiber per megajoule	Encouraged in the well-nourished, but in poorly nourished patients may compromise energy intake
Protein	15–20% of total energy; ~1–2 g/kg/d	200% of reference nutrient intake
Salt	Range 1000–1500 mg/d	Increased requirement: unrestricted intake

CFRD, cystic fibrosis-related diabetes.

with milder CF mutations who are overweight). For patients on insulin therapy, carbohydrate counting is useful for determining the pre-meal insulin dose. Large quantities of sugary beverages such as soda pop may be difficult to adequately cover with insulin and are generally discouraged.

Insulin therapy

Insulin insufficiency is the primary pathologic feature of CFRD, and insulin replacement is the only recommended medical treatment (1). Insulin therapy stabilizes lung function and improves nutritional status in patients with CFRD (9, 72, 81). The general principles of insulin therapy are presented in Table 5. When patients are in their baseline state of health, insulin requirements tend to be modest because of the persistence of endogenous insulin secretion and perhaps because of decreased levels of glucagon (average insulin dose <0.5–0.8 units/kg/d in both adolescents and adults) (82, 83). Patients with fasting hyperglycemia are generally treated with basal-bolus therapy, with an insulin pump or with a combination of long-acting basal insulin and rapid-acting insulin to cover carbohydrates and correct hyperglycemia. In patients with CFRD without fasting hyperglycemia, pre-meal rapid-acting insulin reversed chronic weight loss and is now considered standard care (72). Because of the relation between nutritional status and survival in CF, the anabolic effects of insulin may be the most critical aspect of therapy. Thus, the goal is to provide as high an insulin dose as the patient can safely tolerate.

Oral diabetes agents

Oral diabetes agents are currently not recommended in CFRD. A Cochrane review did not identify any randomized-controlled trials other than the CFRDT Trial (84), where the insulin secretagogue repaglinide was not able to produce sustained weight gain in individuals with CFRD without fasting hyperglycemia

(72). Agents that reduce insulin resistance are unlikely to be effective in CFRD, because insulin resistance is not the major etiological factor. Furthermore, there are problems with currently available insulin sensitizers that might be particularly unacceptable in the CF population, including gastrointestinal side effects (metformin) and osteoporosis (thiazolidinediones). There are no data on the clinical use of incretin mimetic agents such as the glucagon-like peptide-1 (GLP-1) agonists or the dipeptidyl peptidase-4 (dpp-4) inhibitors in CF, but they would not be expected to be good candidates for use in this population given that their mechanism of action includes reducing gastric emptying and decreasing glucagon levels.

Inpatient management of CFRD

During acute illness, CF patients are at increased risk for developing hyperglycemia (85, 86). While data from other populations suggest that intensive insulin therapy may be beneficial in the hospital setting, no studies have examined the benefits of maintaining tight euglycemia in hospitalized CF patients. In those with pre-existing diabetes, insulin requirements are usually much larger during illness: up to four times the usual insulin may be needed. The insulin dose must be quickly reduced as clinical status improves to avoid hypoglycemia, although this may take a couple of months (85). In CF patients who had normal glucose levels prior to becoming ill, blood glucose levels may return to normal after the illness resolves although it is likely that hyperglycemia will occur again with the next acute exacerbation.

Treatment of CF patients with abnormal glucose tolerance

Small, uncontrolled studies suggest that patients with IGT might benefit from insulin therapy (81, 87–89). However, there are no definitive data on the benefits of insulin therapy for CF patients without an actual

Table 5. Principles of insulin therapy in CFRD

General principles	<ul style="list-style-type: none"> • CFRD patients typically require 0.5–0.8 units insulin per kg body weight per day when they are in their usual state of health. Much more may be required during stress. • Because of the catabolic effects of insulin insufficiency, the goal is to give the patient as much insulin as can be safely tolerated. • Choose the insulin regimen that best fits the patient’s lifestyle and meets the needs of their CF management.
Basal insulin	<ul style="list-style-type: none"> • Generally the goal is about 0.25 IU/kg body weight per 24 h; start at half this and adjust upward based on fasting glucose levels.
Meal coverage	<ul style="list-style-type: none"> • A common starting dose is 0.5–1 IU rapid-acting insulin for every 15 g of carbohydrate consumed. Insulin pens or syringes that deliver half units may be needed. • The dose is adjusted by increments of 0.5 IU per 15 g carbohydrate to achieve 2-h post-prandial blood glucose goals. • For very young patients or those who are unsure of what they will eat due to nausea or gastroparesis, the dose may need to be given right after the meal (although before is always better if possible). • Patients with CFRD without fasting hyperglycemia may be managed with pre-meal insulin alone, or with basal alone (depending on patient factors, including eating habits)
Correction dose (Sensitivity)	<ul style="list-style-type: none"> • Pre-meal correction is usually started at 0.5–1 IU rapid-acting insulin for every 2.8 mmol/L (50 mg/dL) above 8.3 mmol/L (150 mg/dL) and adjusted as needed.
Coverage of overnight drip feeding	<ul style="list-style-type: none"> • Frequently a single dose of regular/soluble plus NPH (e.g., Humulin N, Protaphane, Novolin N, Insulatard, Isophane, etc) insulin will cover an overnight drip feeding. The regular insulin covers the first half and the NPH the second half of the feeding. • Starting dose: calculate the total grams carbohydrate in the feeding, determine a total insulin dose based on the insulin to carbohydrate ratio (typically 0.5–1 units per 15 g), and deliver half of this as regular and half as NPH insulin. • Glucose levels 4 h into the feeding are used to adjust the regular insulin dose and those at the end of the feeding to adjust the NPH insulin dose. Occasionally a little rapid-acting insulin is also needed at the beginning. • Think of this as a ‘long meal’. It does not replace basal insulin, and patients should only take this insulin when they have the feeding.
Limited care in a resource poor setting	<ul style="list-style-type: none"> • When analog insulin is not available, NPH insulin (e.g., Humulin N, Protaphane, Novolin N, Insulatard, Isophane, etc) and regular/soluble insulin can be used to treat CFRD, but care needs to be taken to avoid late post-prandial hypoglycemia. One possible regimen is NPH insulin at bedtime, and regular insulin with breakfast, lunch, and supper, in a patient who is eating three meals and three snacks a day.

CFRD, cystic fibrosis-related diabetes

diagnosis of diabetes. This has been identified as a high-priority research question (1).

Recommended care

ISPAD endorses the 2010 recommendations sponsored by the American Diabetes Association and the Cystic Fibrosis Foundation and endorsed by the Pediatric Endocrine Society, published as an American Diabetes Association Position Statement (1).

Diagnosis

- The onset of CFRD is defined as the date a person with CF first meets diabetes diagnostic criteria, even if hyperglycemia subsequently abates. [E, Consensus]

- During a period of stable baseline health the diagnosis of CFRD can be made in CF patients according to standard ADA criteria. [E, Consensus]

- FPG ≥ 126 mg/dL (7.0 mmol/L), or
- 2-h OGTT plasma glucose ≥ 200 mg/dL (11.1 mmol/L), or
- HbA1c ≥ 48 mmol/mol (6.5%) (HbA1c below this does not exclude CFRD), or
- Random glucose ≥ 200 mg/dL (11.1 mmol/L) with symptoms

- The diagnosis of CFRD can be made in CF patients with acute illness (intravenous antibiotics in the hospital or at home, systemic glucocorticoid therapy) when fasting plasma glucose (FPG) levels ≥126 mg/dL (7.0 mmol/L) or 2-h post-prandial

plasma glucose levels ≥ 200 mg/dL (11.1 mmol/L) persist for more than 48 h. [E, Consensus]

- The diagnosis of CFRD can be made in CF patients on enteral continuous drip feedings when mid- or post-feeding plasma glucose levels exceed 200 mg/dL (11.1 mmol/L) on two separate days. [E, Consensus]
- Diagnosis of gestational diabetes should be made based on the recommendations of the International Association of Diabetes and Pregnancy Study Group (90) where diabetes is diagnosed based on 0, 1, and 2-h glucose levels with a 75-g OGTT if any one of the following is present:
 - FPG ≥ 92 mg/dL (5.1 mmol/L)
 - 1 h plasma glucose ≥ 180 mg/dL (10.0 mmol/L)
 - 2 h plasma glucose ≥ 153 mg/dL (8.5 mmol/L)
- CF patients with gestational diabetes are not considered to have CFRD, but require CFRD screening 6–12 wk after the end of the pregnancy. [E, Consensus]
- Distinguishing between CFRD with and without fasting hyperglycemia is not necessary. [B]

Screening

- The use of HbA1c as a screening test for CFRD is not recommended. [B]
- Screening for CFRD should be performed using the 2-h 75 g (1.75 g/kg) OGTT. [E, Consensus]
- Annual screening for CFRD should begin by age 10 in all CF patients who do not have CFRD. [B]
- CF patients with acute pulmonary exacerbation requiring intravenous antibiotics and/or systemic glucocorticoids should be screened for CFRD by monitoring fasting and 2-h post-prandial plasma glucose levels for the first 48 h. [E, Consensus]
- Screening for CFRD by measuring mid- and immediate post-feeding plasma glucose levels is recommended for CF patients on continuous enteral feedings, at the time of gastrostomy tube feeding initiation and then monthly at home. Elevated glucose levels detected by SMBG must be confirmed by a certified laboratory. [E, Consensus]
- Women with CF who are planning a pregnancy or confirmed pregnant should be screened for pre-existing CFRD with a 2 h 75-g fasting OGTT if they have not had a normal CFRD screen in the last 6 months. [E, Consensus]
- Screening for gestational diabetes is recommended at both 12–16 wk and 24–28 wk gestation in pregnant women with CF not known to have CFRD, using a 2 h 75-g OGTT with blood glucose measures at 0, 1, and 2 h. [E, Consensus]
- Post-pregnancy screening for CFRD using a 2-h 75 g fasting OGTT is recommended 6–12 wk after the

end of the pregnancy in women with gestational diabetes (diabetes first diagnosed during pregnancy). [E, Consensus]

- CF patients not known to have diabetes who are undergoing any transplantation procedure should be screened pre-operatively by OGTT if they have not had CFRD screening in the last 6 months. Plasma glucose levels should be monitored closely in the peri-operative critical care period and until hospital discharge. Screening guidelines for patients who do not meet diagnostic criteria for CFRD at the time of hospital discharge are the same as for other CF patients. [E, Consensus]

Management of CFRD

- Patients with CFRD should ideally be seen quarterly by a specialized multidisciplinary team with expertise in diabetes and CF. [E, Consensus]
- Patients with CFRD should receive ongoing diabetes self-management education from diabetes education programs that meet national standards. [E, Consensus]
- CF patients with CFRD should be treated with insulin therapy. [A]
- Oral diabetes agents are not as effective as insulin in improving nutritional and metabolic outcomes in CFRD, and are not recommended outside the context of clinical research trials. [A]
- Patients with CFRD who are on insulin should perform self-monitoring of blood glucose at least three times a day. For many patients, four to eight or more times a day is appropriate, depending on meal pattern, exercise, intestinal concerns such as gastroparesis, and acute state of health. [E, Consensus]
- Patients with CFRD should strive to attain plasma glucose goals as per the ADA recommendations for all people with diabetes, bearing in mind that higher or lower goals may be indicated for some patients, and that individualization is important. [E, Consensus]
- HbA1c measurement is recommended quarterly for patients with CFRD to guide insulin therapy decisions. [E, Consensus]
 - For most patients with CFRD the HbA1c treatment goal is $< 7\%$ (53 mmol/mol) to reduce the risk of microvascular complications, bearing in mind that higher or lower goals may be indicated for some patients, and that individualization is important. [B]
- CF Foundation evidence-based guidelines for nutritional management of all persons with CF

are recommended for patients with CFRD. [E, Consensus]

- Patients with CFRD should be advised to do moderate aerobic exercise for at least 150 min/wk. [E, Consensus]

Complications

- Education about the symptoms, prevention, and treatment of hypoglycemia, including the use of glucagon, is recommended for patients with CFRD and their care partners. [E, Consensus]
- Patients with CFRD should have their blood pressure measured at every routine diabetes visit as per ADA guidelines. Patients found to have systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg or >90 th percentile for age and gender for pediatric patients should have repeat measurement on a separate day to confirm a diagnosis of hypertension. [E, Consensus]
- Annual monitoring for microvascular complications of diabetes is recommended using ADA guidelines, beginning 5 yr after the diagnosis of CFRD or, if the exact time of diagnosis is not known, at the time that fasting hyperglycemia is first diagnosed. [E, Consensus]
- Patients with CFRD diagnosed with hypertension or microvascular complications should receive treatment as recommended by the ADA for all people with diabetes, except that there is no restriction of sodium and, in general, no protein restriction. [E, Consensus]
- An annual lipid profile is recommended for patients with CFRD and pancreatic exocrine sufficiency, or if any of the following risk factors are present: obesity, family history of coronary artery disease, or immunosuppressive therapy following transplantation. [E, Consensus]

Conflict of interest

The authors have declared no relevant conflicts of interest.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Diabetes education in children and adolescents

Lange K, Swift P, Pankowska E, Danne T. Diabetes education in children and adolescents. *Pediatric Diabetes* 2014; 15 (Suppl. 20): 77–85.

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Executive summary and Recommendations

Education is the key to successful management of diabetes (E). There is evidence that educational interventions in childhood and adolescent diabetes have a beneficial effect on glycemic control and on psychosocial outcomes (A).

To maximize the effectiveness of both conventional diabetes treatment and the advances in diabetes management and technology (especially self-monitoring of blood glucose, analog insulin, insulin pumps, continuous glucose monitoring), it is advisable that quality-assured structured education is available to all young people with diabetes and their carers (E).

An interdisciplinary education team sharing the same philosophy and goals and speaking ‘with one voice’ has beneficial effects on metabolic and psychosocial outcomes (B).

Health care professionals require appropriate specialized training in the principles and practice of teaching and education to implement successfully behavioral approaches to education designed to empower young people and carers in promoting self-management (E).

The content and delivery of structured education needs regular review to enable it to evolve to suit individuals, local practice and the changes in diabetes management and technology (E).

Educational interventions which have been shown to be most effective are most likely to:

- be based on clear theoretical psycho-educational principles (E)
- be integrated into routine clinical care (e.g., as an essential integral part of intensive insulin management) (A)
- be referred to as an ongoing process of provision of individualized self-management and psychosocial support (E)
- involve the continuing responsibility of parents and other carers throughout adolescence (B)
- make use of cognitive behavioral techniques most often related to problem-solving, goal setting, communication skills, motivational interviewing, family conflict resolution, coping skills, and stress management (A)
- use new technologies in diabetes care as one of the vehicles for educational motivation (A)

In the evaluation of structured educational programs it is essential to focus on outcomes such as the patient's achievement of self-selected diabetes-care goals, improved psychosocial adaptation, and enhanced self-efficacy in addition to glycemic control (E).

Education is the keystone of diabetes care and structured self-management education is the key to a successful outcome (1). National pediatric guidelines emphasize the importance of education, and most of them include specific chapters on education and educational principles (2–9). Publications which provide useful guidelines on diabetes education include the 'National Standards for diabetes self-management education (DSME)' (2), the 'Position statement on structured education' (10), the 'International Curriculum for Diabetes Health Professional Education' (11), the 'Recommendations for age-appropriate education of children and adolescents with diabetes and their parents in the European Union' (12), the 'Good practice recommendations on pediatric training programs for health care professionals in the EU' (13), and 'The pediatric diabetes toolbox for creating centres of references' (14).

The following definition of Diabetes Education has been proposed: *'The process of providing the person with the knowledge and skills needed to perform diabetes self-care, manage crises, and to make lifestyle changes to successfully manage the disease'* (15). Education may be seen as an interface between clinical practice and research. Research into diabetes and educational methods is important in improving clinical practice (2–5, 7, 8), and this should be the responsibility of each nation/state and be a national priority (7, 8, 11–13).

Educational programs must be carefully planned, have specific aims, and learning objectives, which are shared with people with diabetes, their families, and other caregivers of young people with diabetes (2, 4, 5, 12, 14). It has remained contentious whether educational interventions *per se* are beneficial in diabetes care, particularly in children and adolescents because *'educational, psychosocial and psychotherapeutic interventions are frequently combined for the purpose of improving knowledge, skills and self-efficacy across various aspects of diabetes self-management'* (15). However, the success of an intensified insulin therapy in children and adolescents mainly depends on the knowledge, self-management skills, and on the motivation of the whole family (2, 3, 8, 12).

Nevertheless, systematic reviews of psycho-educational interventions conclude that such measures have small to medium beneficial effects on glycemic control (16–21) and a somewhat greater effect on psychological outcomes (22, 23). The effects are more pronounced for children than for adults (22). Educational efforts are most effective when integrated into

routine care and are delivered with the involvement of parents. In addition, promoting empowerment principles, techniques for problem-solving, goal setting, and self-efficacy improve the efficacy of psycho-education (2, 4, 7–9, 12, 14, 16, 18, 24, 25).

The DCCT provided unequivocal evidence that intensification of management reduces microvascular complications and that intensification requires effective diabetes self-management. Most importantly, effective self-management requires frequent and high levels of educational input and continuing support to young patients as well as to their parents and other caregivers (26, 27). Furthermore, health care professionals engaged in education who are perceived by young people as being 'motivating' may eventually encourage greater adherence to therapy (28). This high level of motivation and enthusiasm by those delivering the educational intervention is likely to improve biomedical outcomes by itself and makes interpretation of educational research a complex science (24, 29).

In contrast, those people who do not receive education or do not continue to have educational contacts are more likely to suffer from diabetes-related complications (2, 5, 29–31). It is a concern, however, that parents and adolescents often express satisfaction about services received even when there may be large gaps in education, psychological support, and self-management techniques accounting for relatively unsatisfactory and variable metabolic control (32).

Universal principles

Every young person has a right to comprehensive expert structured education which should empower them and their families to take control of their diabetes (1–8).

Children and adolescents, both of their parents (8, 14, 33), and other care providers should all have easy access to and be included in the educational process. Also care givers in nurseries or kindergarten and teachers in school should have access to an appropriate structured diabetes education (14, 34).

Diabetes education should be delivered by an interdisciplinary team of health care professionals with a clear understanding of the special and changing needs of young people and their families as they grow through the different stages of life (1, 2, 5, 8, 13, 14, 24). Diabetes education needs to be adaptable and personalized so that it is appropriate to each individual's age, stage of diabetes, maturity, and lifestyle, culturally sensitive and at a pace to suit individual needs (1, 2, 4, 5, 8, 12).

The priorities for health care professionals in diabetes education may not match those of the child and family. Thus diabetes education should be based on a thorough assessment of the person's attitudes,

beliefs, learning style, ability and readiness to learn, existing knowledge, and goals (1).

Educators (pediatric endocrinologist or physician trained in the care of children and adolescents with diabetes, diabetes educators, dieticians, psychologists, social workers, and other health care providers) should have access to continuing specialized training in current principles of insulin therapy, new diabetes technologies, advances in diabetes education, and educational methods (2, 4, 5, 8, 12–14, 24).

Diabetes education needs to be a continuous process and repeated for it to be effective (2–14).

Content and organization of education programs

It is widely accepted that diabetes cannot be successfully managed without behavioral modification (35, 36). Health professionals need to understand that education alone focusing only on acquisition of knowledge is unlikely to alter behavior particularly in those individuals where diabetes appears to be overwhelmingly difficult. Thus the diabetes team needs training not only in the principles of teaching and structured education but also in behavioral change management including counseling techniques (2, 35, 36).

The importance of structured education (12, 14) programs has been emphasized in a variety of contexts. Evidence comes mainly from adult diabetes that it is more effective than informal unstructured education in improving metabolic control (15, 17, 37, 38). In pediatric diabetes, systematic studies of structured educational programs are rare and research has focused more on psychosocial interventions. However, there are ethical and methodological limitations of performing randomized-controlled trials (RCTs) on initial diabetes education at onset. The evidence for efficacy of these interventions comes from studies performed mainly in North America, Australia, and Europe and has been extensively reviewed in various publications (14, 15, 17–21, 39, 40).

There are four key criteria which characterize a structured educational program (10, 12):

- 1 it has a structured, agreed, written, and evaluated curriculum
- 2 it uses trained educators
- 3 it is quality assured
- 4 it is audited

Moreover, to put this into practice it has been recommended that (1–14):

- Structured education should be available to all people with diabetes at the time of initial diagnosis, or when it is appropriate for them, and then as

Table 1. Principles and practice of education in children, adolescents, and their parents/primary care givers

1. Motivation	- The learner needs to and/or have a desire to learn
2. Context	- Where is the learner now? - Where does the learner want to be later?
3. Environment	- Learner-centered, comfortable, trusting - enjoyable/entertaining/interesting/'open'
4. Significance	- Meaningful, important, links, or joins up - reward or gain
5. Concepts	- Simple to complex in gentle steps (<i>short attention span</i>)
6. Activity	- Constantly interactive - practical (<i>fitting into real life</i>) - goal setting and problem-solving
7. Reinforcement	- Repetition, review, summarize
8. Reassess, evaluate, audit	
9. Move forward (<i>continuing education</i>)	

required on an ongoing basis, based on a formal, regular individual assessment of need.

- Education should be provided by an appropriately trained interdisciplinary team. The team should have a sound understanding of the principles governing teaching and learning.
- Interdisciplinary teams providing education should include, as a minimum, a pediatric endocrinologist/diabetologist or a physician trained in the care of children and adolescents with diabetes, a diabetes specialist nurse/diabetes educator and a dietician. Furthermore, a psychologist and a social worker are recognized as mandatory in the interdisciplinary team (12).
- Sessions should be held in a location accessible to individuals and families, whether in the community or the inpatient center.

Educational programs should use a variety of teaching techniques, adapted – wherever possible – to meet the different needs, personal choices, learning styles of young people with diabetes and parents, as well as local models of care.

Table 1 summarizes the philosophy of education in children, adolescents, and parents with diabetes (2, 14, 39–41; Table 1). In addition, the generally accepted principles which govern quality in teaching should also be recognized by diabetes educators (41) (Table 2).

Primary (level 1) education

The following topics are recommended at diagnosis as a comprehensive basis for successful therapy and positive emotional coping from onset on throughout lifetime for young patients and their families:

- 1 Explanation of how the diagnosis has been made and reasons for symptoms
- 2 Simple explanation of the uncertain cause of diabetes. No cause for blame or feelings of guilt

Table 2. Qualities looked for by UK Office for Standards in Education – OFSTED (39)

-
- Lessons should be purposeful with high expectations conveyed
 - Learners should be given some opportunities to organize their own work *[over direction by teachers needs to be guarded against]*
 - Lessons should elicit and sustain learner's interest and be perceived by pupils to be relevant and challenging
 - The work should be well matched to learner's abilities and learning needs
 - Learner's language should be developed and extended *[teachers' questioning skills play a part here]*
 - A variety of learning activities should be employed
 - Good order and control should be largely based on skillful management of learner's involvement in the lesson and mutual respect
-

- 3 The need for immediate insulin and how it will work
- 4 What is glucose? – normal blood glucose (BG) levels and glucose targets
- 5 Practical skills
 - insulin injections/pump therapy if indicated/insulin dose adjustment
 - blood and/or urine testing and reasons for monitoring, CGM (continuous glucose monitoring) if indicated
- 6 Basic dietetic advice inclusive carb counting, healthy eating
- 7 Explanation of hypoglycemia (symptoms, prevention, management)
- 8 Diabetes during illnesses. Advice not to omit insulin – prevent DKA, monitoring ketones
- 9 Diabetes at home or at school including the effects of exercise
- 10 Identity cards, necklets, bracelets, and other equipment
- 11 Membership of a Diabetes Association and other available support services
- 12 Psychological adjustment to the diagnosis (parents and children)
- 13 Integration of diabetes self-management therapy into family life and social activities
- 14 Details of emergency telephone contacts and continuous long-term care

Some guidelines discuss the 'controversy' (6, 8) between in-hospital and ambulatory education at diabetes onset. Owing to the heterogeneity of health care systems and funding of diabetes care and education there is evidence supporting both alternative approaches (40, 42–46).

Methods of delivering primary levels of education and the use of educational resources will depend on local experience, facilities, and the respective national health care system (12, 14). It will be dominated

initially by individual (family) teaching, but specific age appropriate curricula for children of different cognitive levels and adolescents as well as special curricula for parents are developed and evaluated in some countries (12, 14, 39, 40).

Health professionals should learn to incorporate and deliver the education using behavioral approaches which are learner-centered and not didactic (35, 47, 48). All team members should follow a common philosophy and common goals in diabetes education (24).

Initial learning should be reinforced by written guidelines and curricula. It should be accompanied by quality-assured education materials (books, booklets, leaflets, DVDs, websites, games, and others) which should be appropriate to the child's and adolescent's age and maturity (12, 14). All materials should follow common therapeutic goals and a shared holistic approach.

Written materials for parents should use appropriate language and a style that is easily comprehensible (it is suggested that this should be at the level of a popular local or 'tabloid' newspaper). An integrated education concept for parents combines knowledge, practical self-management skills with psychological advice on parental tasks, and emotional support (2–14). For parents with limited literacy and/or poor numeracy special material focusing on diagrams, drawings, video clips, and other visual media are recommended (49, 50).

Secondary (level 2) continuing educational curriculum

Core topics of the continuing curriculum are:

- 1 Pathophysiology, epidemiology, classification, and metabolism
- 2 Insulin secretion, action, and physiology
- 3 Insulin injections, types, absorption, action profiles, variability and adjustments, insulin pump therapy with different boluses and bolus calculation
- 4 Nutrition – food plans; qualitative and quantitative advice on intake of carbohydrate, fat, proteins, and fiber; coping with special events and eating out; growth and weight gain; 'diabetic foods'; sweeteners and drinks, prevention of disordered eating
- 5 Monitoring (glucose, ketone), including glycated hemoglobin and agreed targets of control, use of CGM (if applicable)
- 6 Hypoglycemia and its prevention, recognition, and management including glucagon
- 7 Intercurrent illness, hyperglycemia, ketosis, and prevention of ketoacidosis
- 8 Problem-solving and adjustments to treatment in everyday life, motivation and coping with unexpected glucose fluctuations
- 9 Goal setting

- 10 Micro- and macrovascular complications and their prevention. The need for regular assessment
- 11 Exercise, holiday planning, and travel, including educational holidays and camps
- 12 Smoking, alcohol, and drugs
- 13 Nursery, kindergarten, school, college, employment, and driving vehicles
- 14 Sexuality, contraception, pregnancy, and childbirth
- 15 Updates on research.

Continuing education will take place most often in an ambulatory (outpatient, domiciliary, and community) setting (2–14, 51). Where staffing levels, expertise and local circumstances do not permit this, educational programs may be carried out in the hospital environment, either by individual teaching or in groups and whenever possible in a protected environment encouraging to learning (43, 51).

The educational program should utilize appropriate patient-centered, interactive teaching methods for all people involved in the management of diabetes, particularly the affected child or adolescent (2–14).

A realistic understanding of self-management is a prerequisite for higher levels of diabetes education as both educational and psychosocial issues are important determinants of success (2, 12, 15, 39, 40).

Newer technology may be attractive to young people including videos, CDs, computer games, text messaging for information (52), web 2.0 portal (53), telephone reminders, and support (54) but is used most effectively in interactive modes (5, 15, 19, 55).

Group education may be more cost effective and the educational experience may be enhanced by peer group (37, 38, 51) or school friendships (39). However, there is evidence that education directed at the specific needs of individuals is at least equally effective as group education (56).

There is some evidence that benefit might be gained from participation in organized Diabetes Association meetings and in holiday or camping experiences (57, 58).

Evidence from group discussions with young people suggests that education using these newer technologies is attractive for them, and there is further scientific data to support their widespread use (53, 55).

Education should be viewed as an important factor in empowerment for both parents (33, 42), as well as children and adolescents. This empowerment approach should enable young people to use knowledge and practical skills in problem-solving and self-care, and to be in control of goal setting for better care. In essence, the patients need to experience that they have influence over their own lives in making informed decisions about their diabetes (2–14, 47, 48).

Matching and adjusting insulin profiles to quantified food intake and exercise levels are an important part of

any intensified diabetes management. More complex modern therapeutic regimens with multiple daily injections, use of different insulins and insulin analogs, continuous subcutaneous insulin infusion (CSII, insulin pumps), as well as wearing continuous glucose measurement devices require appropriate education. Higher levels of education and understanding are required for these interventions to be successful and require more time, skill, and greater resources from the educational team (2, 8, 9, 14, 59–61). Changing from one form of insulin regimen to another as the only means of intervention does not improve metabolic control (16, 24, 32). In contrast, by addressing the total management package using comprehensive structured education, the likelihood of success is greater (2–8, 16, 24, 61, 62), especially if the educators are highly motivated (29).

Education and age group

Diabetes education needs to be adaptable and appropriate to each individual's age and maturity (1, 14, 63). Specific curricula and appropriate education materials and tools are recommended for children and adolescents of different age groups (3–5, 5–6, 7–9, 9–12, 13–18 yr, and for young adults as part of a structured transition process) as well as for parents and other primary care givers of young people with diabetes.

Infants and toddlers

- Total dependence on parents and other care providers for injections/management of pumps, food and monitoring and the requirement of a trusting attachment between infant and caregivers (63)
- Mothers may feel increased stress, diminished bonding, and depressive feelings (64–67) but this applies to many chronic diseases (68)
- Unpredictable erratic eating and activity levels
- Difficulties in distinguishing normal infant behavior from diabetes-related mood swings, e.g., due to hypoglycemia (64–67)
- Injections, catheter insertion, and BG checks seen as pain inflicted by caregivers
- Hypoglycemia is more common (see chapter on hypoglycemia). Long standing hyperglycemia may be even more harmful. Education on prevention, recognition, risk, and management are therefore a priority (69, 70).
- Care in nursery and kindergarten

There is conflicting evidence on influencing behavioral characteristics of preschool children with diabetes through education (64, 68) and whether

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their diabetes outcomes depend on them being part of the educational approach. But parents report the importance of education and non-judgmental support from a team (24, 25, 40, 61, 65)

School age children

- Adjusting to the change from home to school, developing self-esteem, and peer relationships (34, 55)
- Learning to help with and developing skills in injections, pump use, and monitoring
- Progressive recognition and awareness of hypoglycemic symptoms
- Increasing understanding and self-management
- Adapting diabetes to school programs, school meals, exercise, and sport
- Including monitoring of BG levels, injections, giving boluses in the school setting
- Advising parents on the gradual development of the child's independence with progressive stepwise hand-over of appropriate responsibilities (1, 63)

School age children have expressed dissatisfaction that health professionals talk to parents and not to them. There is some evidence that focused age appropriate educational interventions are effective in children and families (17–20, 23, 25, 71–74).

Adolescents

(see chapter on Diabetes in Adolescence for references)

- Accepting the critical role of continued parental involvement and yet promoting independent, responsible self-management appropriate to the level of maturity and understanding (72, 74)
- Understanding that knowledge about diabetes in adolescents is predictive of better self-care and (metabolic) control but the association is modest
- Discussing emotional and peer group conflicts
- Discussion weight control and preventing disordered eating (75, 76)
- Teaching problem-solving strategies for dealing with dietary indiscretions, illness, hypoglycemia, blood glucose fluctuation due to puberty, sports, smoking, alcohol, drugs, and sexual health
- Negotiating targets, goals and priorities and ensuring that the tasks taken on by the adolescent are understood, accepted, and achievable (77)
- Understanding that omission of insulin is not uncommon. The opportunity should be grasped for non-judgmental discussion about this
- Developing strategies to manage transition to adult services (78).

In conclusion, age-appropriate, quality-assured structured diabetes education needs to be available to all young people with diabetes and their carers to maximize the effectiveness of both conventional diabetes treatment as well as more advanced diabetes management and technology.

Conflict of interest

KL has received lecture honoraria from Abbott, Bayer Vital, Lifescan, Lilly Deutschland, Menarini, Merck Serono, NovoNordisk, Roche diagnostics, and Sanofi. Furthermore, she received research support from Menarini, Novo Nordisk, and Roche. TD has received honoraria from NovoNordisk, Lilly, Sanofi, Medtronic, Biondi, Becton Dickinson, Boehringer, and Roche. EW and PGFS have declared no conflict.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

The delivery of ambulatory diabetes care to children and adolescents with diabetes

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Executive summary and Recommendations

From the outset, the child or adolescent with diabetes and relevant family should receive care from a multidisciplinary diabetes team comprised of specialists with training and expertise in both diabetes and pediatrics, knowledgeable of child, and adolescent development (E). The Diabetes Care Team should emphasize that the family and child are the central members of the care team (E). Clear and consistent communication around education and the treatment plan is essential. The treatment plan should integrate current technology commensurate with available resources and the individual child's/family's needs (E). The multidisciplinary team is unlikely to be available in areas of low population density and where childhood diabetes rarely occurs. In these circumstances, care is likely to be provided by a locally based pediatrician or general (family) physician, who should have ready access to advice and expertise of the Diabetes Care Team in regional centers of excellence (1–3) (C, E).

The Diabetes Care Team should provide:

Key words: ambulatory care – Diabetes – ISPAD – Pediatric

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- Specialized hospital medical care.
- Expert comprehensive ambulatory care for diabetes and associated pediatric conditions.
- Introduction of new therapies and technologies as diabetes management evolves.
- Expert advice on issues related to diabetes such as exercise, travel, and other special life events.
- Advice for care at school, camps, and other venues where children with diabetes require care when away from home.
- Screening for comorbid conditions, complications, and risk of complications.
- Emergency telephone or other support 24 h a day to patients and families.
- Extra attention, including psychosocial evaluation and support, is needed for children who are 'high-risk', e.g., poor glycemic control [hemoglobin A1c (HbA1c) >8.5% (64 mmol/mol)] and/or frequent urgent visits or hospitalization.
- Advice and support to physicians and healthcare professionals who provide diabetes care where

immediate access to a Diabetes Care Team is not possible (B, E).

Processes of diabetes care should include:

- A visit at least every 3 months for a re-evaluation of diabetes management and review of home management records, as well as evaluation of growth, development, and general health.
- An annual visit with assessment and review of dietary knowledge, self-management skills and behaviors, and psychosocial needs, screening for comorbidities and risk factors for long-term complications, identification of barriers to care, and educational updates.
- A planned transition to adult diabetes care which improves outcomes and helps to ensure continuity of care during this critical time (4, 5) (B, E). The age of transfer to an adult clinic varies according to individual and local circumstances.
- Culturally sensitive communication, counseling, and encouragement for altering preconceptions or negative and unhealthful beliefs about diabetes (6).
- Assistance to access care.

Care is facilitated by electronic or paper tools such as clinic information sheets (E) to track each child's progress and to develop clinic benchmarks to compare to regional and national/international benchmarks for improvement of care (E).

Outcome of care

The Diabetes Care Team should monitor outcomes for their patient population in order to identify areas of structure and process of care that could improve metabolic and other health outcomes (E). Comparing regional and national/international benchmarks is useful for improving outcomes (E) (7).

The ultimate goal is to provide care that results in normal growth and development, high quality of life (QoL), and lowest possible risk of acute and long-term complications. This is best accomplished by helping children and families become proficient in self-management, remain motivated throughout childhood and adolescence and allow children to develop into independent, healthy adults (E).

Cost of care and treatment cost to benefit outcomes data over the child's lifetime are critical to providing optimal care to children with diabetes. A high priority should be given for collecting and providing such information to governments and healthcare agencies. Governments and policy makers must be involved so that adequate resources are provided for high-quality diabetes care. Continuous support from the International Diabetes Federation and other responsible organizations is essential for uninterrupted

care of children in developing countries. Advocacy efforts and community education can promote awareness and understanding of diabetes, improving the safety and well-being of children with diabetes [E].

Introduction

This section of the ISPAD Consensus 2014 Guidelines outlines recommendations for diabetes ambulatory care, including periodic assessments of clinical outcomes, as well as best and emerging practices. Resources and costs are important considerations in processes of care. The availability of resources varies widely among countries, within countries, and among patient populations. Some children have access to new technologies, whereas others have limited access even to insulin and other basic diabetes supplies. Comparisons of ambulatory diabetes care practices and cost effectiveness of care are important areas for which there are limited data. The delivery of care in settings such as schools and camps is also addressed. Specific recommendations for certain elements of ambulatory care, including insulin therapy, assessment and monitoring of glycemic control, nutritional management, diabetes education, screening for and management of microvascular and macrovascular complications, and type 2 diabetes, are addressed in detail elsewhere in the ISPAD guidelines, which should be consulted in conjunction with this chapter.

Diabetes is primarily managed in the outpatient or ambulatory setting. The importance of regular, ongoing ambulatory diabetes care assessment for youth with diabetes is essential to maintain optimal glucose control and to monitor risk factors that predispose to acute and chronic complications. The components of medical care include structure, processes, content, and outcomes. Structure of care describes how delivery systems are organized and financed; processes of care describe how care is delivered; content of care describes what is being delivered, including treatment and education that affect outcomes (8). Intermittent critical re-examination of these components provides an opportunity to continually improve the quality of care delivered using available tools and resources. Because diabetes is a chronic disorder, approaches to all aspects of medical care, undoubtedly, will change over time. It may also be helpful to review guidelines from other organizations, both national and international (9).

Structure of care

The goal of treatment is to promote a high QoL, normal growth and development, and avoidance of severe short- and long-term complications. The insulin regimen should, ideally, mimic physiologic insulin

secretion and aims to restore normal metabolism. Insulin affects the metabolism of carbohydrate, protein, and fat, and is necessary for normal growth. The main aim of daily insulin treatment is to achieve good glycemic control without undermining the psychological health of the patient and family. Striving for normoglycemia, i.e., maintaining plasma glucose concentrations near to or within the narrow physiologic range is extremely demanding but essential for optimal health outcomes. People with type 1 diabetes (T1DM) who fail to take sufficiently good care of their health can, in the long term, suffer severe complications that can gravely impair quality and length of life (10). These complications of diabetes also lead to substantial societal costs, and the high prevalence of the disease makes it a big public health challenge. Both the ethical and economic consequences are further aggravated by the fact that T1DM generally appears at an early age. It is a challenging task to educate and support effective self-care among children and adolescents with T1DM and their caregivers, not least those with a non-privileged and minority social background. Disparities in care and outcomes exist – less intensive treatments, poorer glucose control, and increased rates of DKA are reported in less advantaged children (11–14).

Healthcare staff should strive to determine each young person's status regarding risk perception, knowledge, perceived control, as well as perceived benefits and costs of health behavior. The diabetes team must use age-appropriate educational tools and the child must be treated in the context of her psychosocial environment, which requires the multidisciplinary team to have a high level of cultural competence.

Diabetes care is best delivered by a multidisciplinary team. The team should consist of:

- Pediatrician specializing in diabetes or endocrinology (preferred), or physician with a special interest (and training) in childhood and adolescent diabetes.
- Diabetes nurse specialist or diabetes nurse educator.
- Dietician (or nutritionist).
- Pediatric social worker with training in childhood diabetes and chronic illness.
- Psychologist trained in pediatrics and with knowledge of childhood diabetes and chronic illness (12).

From the day of diagnosis, it should be emphasized that the immediate family and child are the central members of the care team. School nurses, day care staff, teachers, and others who care for children often play an important role in the child's diabetes care, and may serve as a liaison between the child and the medical team.

A multidisciplinary team is unlikely to be available in areas of low-population density and where childhood diabetes rarely occurs. In these circumstances, care

usually is provided by a local pediatrician or general (family) practitioner, who should have ready access via electronic means of communication to the Diabetes Care Team at a regional center of excellence (13–15).

- General aims of the Diabetes Care Team should be to provide individualized care that best meets the needs of the child and family.
 - An understanding of and support for the psychosocial needs of the child and family, aiding in the child's and family's adjustment to age-appropriate self-management of diabetes.
 - Expert practical guidance and skill training.
- Consistent repeated diabetes education and self-management training.
- Up-to-date advice on insulin management, blood glucose (BG), and ketone monitoring techniques, and monitoring comorbidities, risk factors of complications, and complications. Consistent and sensitive articulation of individualized biochemical goals (BG and HbA1c targets). A consistent philosophy concerning glycemic targets within the diabetes team and within the family influences HbA1c outcomes (15). Contact with other children and families with diabetes and support groups.
- Current information on research in diabetes for patients and regional physicians.
- Ongoing contributions to advancing clinical practice through the optimal application of existing and new technology and the development and evaluation of new technologies.

Diabetes requires skilled self-management in the home and local environment. The Diabetes Care Team should have the resources to develop strong links, effective communication, and shared practices with:

- The child and family at home, and extended family members or guardian.
- The young person at day care, school, or college/university.
- Primary healthcare providers.
- Pediatricians and other healthcare providers in areas of low population density/low diabetes prevalence.

The organization of the Diabetes Care Team, its size, and its location will depend on geographical and demographic characteristics. In general, for members of the pediatric diabetes team to obtain sufficient experience, the number of patients should be at least 150. The number of practitioners depends on local circumstances; a suggested guide to optimal resource allocation per 100 patients: 1.0 diabetes nurse, 0.75

pediatric diabetologist, 0.5 dietitian, and 0.3 social worker/psychologist (16).

Teams from district or regional centers often organize outreach clinics to accommodate children and families living in remote areas. Adequate resources are needed to sustain such services (14, 15).

- In some areas, two-way telecommunication utilizing video – computer technology and local medical staff to facilitate the telemedicine visit allows for more efficient and effective distant care (13, 17, 18).

Computer interfacing with BG meters, continuous glucose sensors, insulin pumps, and insulin pens allows patients to interact directly with the Diabetes Team between visits, which may improve diabetes management (16–18).

- Appropriate reimbursement must be available to support these essential non-face-to-face services in order to insure that Diabetes Care Teams can afford to sustain the use of these technologies (13).

Processes of care

Generally accepted good clinical practice for the successful management of children and adolescents with diabetes includes the following:

At onset

Easy access (24 h a day) for rapid diagnosis and initiation of treatment with availability of written protocols for management of diabetic ketoacidosis (DKA) and other presentations of childhood diabetes (19, 20).

- Provision of practical care guidance at diagnosis includes the education required to enable the family to feel confident to provide diabetes care at home and have a basic understanding of the pathophysiology of diabetes and its treatment. It is important to create a partnership between the care providers and the child and family allowing for shared decision-making and a long-term relationship based on trust.
- Psychosocial support for the child and family. This includes identifying and addressing detrimental health beliefs, e.g., the team may need to provide reassurance that diabetes is not contagious, so the child does not need segregation.
- Written and/or pictorial age-appropriate materials in a format and language the family understands.

Ambulatory management of children at the time of diagnosis is possible in some centers with appropriate resources, but can only be recommended when

members of the Diabetes Care Team are experienced in the outpatient initiation of insulin therapy, management, and education, and adequate reimbursement for ambulatory diabetes team care is available. Hospital facilities must also be available in case of metabolic deterioration.

The importance of providing ‘a good start’ with clear, positive messages, support, and advice, cannot be overemphasized. Education and proactive discussion around common problems that can occur, such as insulin omission, may help decrease the risk of such problems arising later.

Diabetes is an expensive condition to manage. The treatment regimen prescribed from the onset should be appropriate for the family’s economic and educational status. For example, regular and NPH insulin is far less costly than analogs; insulin vials cost less than cartridges for use in pens, meters that use less expensive strips can be as accurate as those with advanced features. Insulin syringes and testing lancets can be reused for the same person with reasonable care. These and other cost saving methods should be advised to families who have limited means (1, 2).

Pictorial educational materials and simple instructions are essential for illiterate families. It is also important to address practical issues around home diabetes management. A person testing BG and injecting insulin several times a day would inevitably generate huge numbers of ‘sharps’ (needles and lancets) on a regular basis. Families must be taught and frequently reminded to safely dispose of these sharps. This can be done in a variety of ways, appropriate to the local conditions. If nothing else is available, parents can be asked to collect all sharps in a thick-walled metal or plastic container (e.g., shampoo bottle) and bring them on each visit to the clinic for safe disposal (3). Insulin cannot be exposed to extreme temperatures. After purchasing the insulin, the family must be taught how to transport and store it. Insulin inadvertently frozen must be discarded. At the other extreme, insulin becomes less potent after exposure to warm temperatures: at temperatures of 32 and 37°C, loss of potency started after 3 wk, whereas at 25–26°C, potency was retained by the end of 4 wk. In areas where ambient temperatures may be as high as 45–48°C, and where refrigeration is not available, insulin can safely be stored in local cooling devices (see Fig. 1) with which temperatures of about 25–26°C can be achieved (19, 20). Poor glycemic control may be due to using insulin that has lost its potency, but this is often overlooked.

The first 6–12 months

- In the first months to year after diagnosis, many children experience a partial remission and insulin

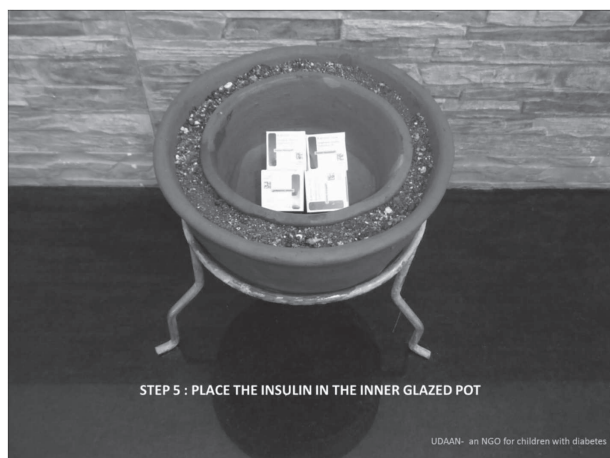


Fig. 1. “Home remedy” for insulin storage courtesy of Dr Archana Sarda, Aurangabad, India.

requirements may decrease dramatically. Frequent contact with the Diabetes Care Team is necessary to help manage the changing insulin requirements typical of the early phases of diabetes. Contact may occur through frequent clinic visits, home visits, and telephone or other methods of communication. Depending on local circumstances, contact often occurs through a combination of these methods.

- Insulin treatment should not be discontinued even if the insulin requirement is very low, and patients should be encouraged to continue to perform regular daily self-monitoring of blood glucose (SMBG).
- Screening for a cognitive or mental health disorder soon after diagnosis will identify individuals (either child or caregivers) at higher risk of being non-adherent to self-care. Five–ten percent of all children suffer from a neurocognitive disorder and at least 2% from a psychiatric disorder. The combination of a cognitive or mental health disorder with diabetes or the presence of a psychiatric disorder in a parent/care giver increases the likelihood of inadequate or incorrect self-care. These patients need special attention and treatment.

Ongoing diabetes care

It is common practice for the diabetes care of children and adolescents to be reviewed in an outpatient clinic every 3 months, or more often if difficulties in managing diabetes are recognized or the child is very young. Outpatient visits with members of the Diabetes Care Team should include assessment of the following:

- General health and well-being.
- Height, weight, and body mass index (BMI) (data recorded and tracked on appropriate growth charts, on which mid-parental height is marked). Weight status can give a general indication of glycemic

control, with weight loss suggesting elevated blood sugars.

- Blood pressure with reference to age-appropriate normal levels.
- Physical examination should include thyroid gland, cardiac, abdominal (for hepatomegaly), feet (for corns, ingrown toenails, and other lesions as well as neurological function, e.g., light touch, vibration sense), and skin, especially injection, catheter insertion, and self-monitoring sites, for evidence of lipo-hypertrophy, lipoatrophy, or infection. Providers should reinforce rotation of injection or catheter insertion sites.
- Insulin types, doses, and injection/insulin delivery devices. Adequacy of storage and transport of insulin, injection technique and, if insulins are being mixed, mixing technique.
- Insulin adjustments for BG values, food, and exercise.
- Glycemic control, including HbA1c and analysis of home glucose monitoring data (glucose meter readings, continuous glucose monitoring (CGM), urine glucose/ketone monitoring, symptoms of nocturia and hypoglycemia). Check glucose values stored in the glucose meter memory for accuracy of information reported by parents/child. The HbA1c and home monitoring should be used in a complementary fashion to assess glycemic control: a lower HbA1c which is due to recurrent hypoglycemia does not mean better glycemic control! Regularly check home glucose meters for accuracy with a reference method of plasma glucose measurement at the clinic, particularly if glucose meter values are not consistent with HbA1c. Home-based meters can differ by 10–15% or more from a laboratory measurement.
- Assess hypoglycemia history, including determination of hypoglycemia awareness, method of treating hypoglycemia, and access to glucagon.
- Intercurrent health problems (infections, enuresis/nocturia, diabetes-related emergency and hospital/emergency visits, and other pediatric and developmental problems).
- Changes in developmental performance, education (particularly school absences/behavioral problems), leisure and sport activities, and psychosocial progress.
- Symptoms relevant to associated comorbid conditions, such as fatigue or abdominal pain that might suggest hypothyroidism or celiac disease, respectively. In the presence of symptoms or signs, given the predisposition to autoimmune conditions, additional evaluation may be indicated. For example, with weight loss, anorexia, unexplained hypoglycemia or decreasing insulin requirements, look for hyperpigmentation and consider evaluating the patient for

possible primary adrenocortical insufficiency (cortisol, perhaps ACTH and 21-hydroxylase antibodies). If a goiter is present, consider evaluating thyroid function [thyroid stimulating hormone (TSH), free or total T4 and perhaps thyroid peroxidase antibodies].

- New health conditions, including disordered eating behavior.
- All current medications and supplements.
- Diabetes-specific knowledge appropriate to the age of the patient, including the family's knowledge of ongoing diet and insulin dose adjustments, sick day management, when and how to monitor for ketosis to prevent ketoacidosis; and recognition of situations that increase the risk of hypoglycemia and how to prevent and treat hypoglycemia.

The outcome of each visit should include:

- An individualized plan of diabetes care incorporating the particular needs of each child/adolescent and family designed to optimize the child's diabetes outcome. This plan may include updated specific calculations for carbohydrate counting and insulin sensitivity (correction doses for hyperglycemia and BG targets).
- A written copy of the plan is provided to the family at the conclusion of the visit outlining any changes made to the child's diabetes management, including results of HbA1c measurement (including individual HbA1c target) and screening tests for comorbidities.
- Motivational discussion including the family's and child's understanding of general treatment goals and an understanding of the medical rationale behind these, e.g., good glycemic control is associated with lower risk of microvascular and macrovascular complications. Because children and adolescents find problems occurring in the distant future difficult to comprehend, immediate benefits of good control (looking better, feeling better, better academic performance, greater ability to make occasional modifications in diet) may be more effective incentives.

It is good practice to provide an annual review of care that includes:

- Physical development and well-being with particular emphasis on growth and pubertal development, BG testing and insulin injection sites, and/or cannula insertion sites for pump or CGM users.
- Additional new pertinent family history (e.g., new diabetes or other endocrine diagnoses, cardiovascular events/diagnosis).
- Review of diabetes care goals.

- Assessment by a diabetes nurse educator of diabetes-specific knowledge appropriate to the age of the patient, and the family's diabetes knowledge.
- Assessment of the family's and child's adjustment to diabetes and age-appropriate transfer of responsibility for self-care to the older child/adolescent.
- Determination of barriers to successful diabetes management, including needle fears, fear of hypoglycemia (parent and child) misconceptions about diabetes (e.g., diabetes is not transmitted by contact), financial condition, interaction with family members and other significant persons, and concealment of diabetes in important situations (sports, driving, etc.).
- Assessment as to whether the diabetes care plan is optimally intensified, taking the above assessments into consideration.
- Review by a nutritionist of the nutritional plan and dietary management. Parents may be encouraged to bring a food diary recording the last few days' diet to inform the consultation with a dietitian about individualized dietary advice and insulin dose adjustment.
- Review of physical activity and adjustments made in therapy for activity.
- Psychosocial assessment (e.g., single vs. two-parent, joint families, sibling issues, household stability, marital stress, parental support, discrimination at school or work place)
- Education concerning the need for routine dental care. Adults with diabetes have a higher incidence of gingivitis and periodontitis compared to the general population (21, 22). Poor glycemic control in children and adolescents has been associated with higher salivary glucose levels and more caries (23).
- Screening for depression and disordered eating.
- Reinforcement of age-appropriate information.
- For adolescents, review of precautions is necessary for safe driving, adverse effects of tobacco, alcohol, marijuana and other substances, sex and contraception, and preconception counseling. It is often appropriate to request parents/care givers to wait in another room so that these topics can be discussed candidly with the adolescent.
- Review of all current medicines and supplements, including complementary and alternative therapies.
- Assessment of understanding the risks of complications and care plans to minimize these risks.
- Assessment of comorbidities. This includes screening for thyroid dysfunction and celiac disease in asymptomatic children, with an annual TSH, and measurement of tissue transglutaminase antibodies every 2 yr.
- Screening for complications and comorbidities from 10 yr of age with greater than 2 yr of diabetes duration, including blood pressure review and urine

microalbumin measurement and ophthalmologic evaluation. Lipid screening at puberty (12 yr of age) and then every 5 yr if within the acceptable risk range, or annually if not within this range [further details on complications screening are available (see reference 16)]. For children with a family history of a lipid disorder, screening should occur 6 months after diagnosis. Screening at diagnosis is less useful, as lipid abnormalities are common at diagnosis and improve once glycemic control improves. If risk factors for complications are found, additional evaluation and treatment may be indicated (5).

Evaluation of patient's home diabetes records – at diabetes care visits and between visits

The patient and his/her family should be praised for performing home glucose monitoring, and the record should never be used to criticize the child or family for failing to reach glucose targets. The records should be used as a tool to identify patterns and trends, identify and solve problems, and to teach diabetes self-management skills. Parents must be counseled to avoid condemning the child for values which are high or low. When possible, a glucose meter that stores glucose values should be used, as this allows for cross-checking to ensure that the values reported are genuine. It is not unusual for the parents or the child to write fictitious values, and care must be taken not to base dose changes on such values. Providers should explore barriers to testing and recording of true results.

There are many models of care that aim to improve communication of home glucose monitoring records, insulin dosing, dietary, and exercise information between the child/adolescent, family, and the diabetes team. It is important to emphasize to the child and family that the adjustments in insulin doses are often needed between clinic visits. The family should be encouraged to review and attempt to analyze the data before contacting the diabetes team for advice.

Examples of useful clinical management tools include:

- Personal handwritten records, monitoring diaries, or logbooks.
- Electronic personal data records. Several apps are now available.
- BG meters with memory capacity (\pm computer/telephone links).
- Continuous glucose sensors with memory capacity (\pm computer links).

The ability to download data from glucose meters, insulin pens, pumps, and continuous glucose monitors provides valuable insight into home management. These data often allow the diabetes team to identify

areas where adjustments need to be made in diabetes care plans and, more importantly, to identify areas where the young patient needs additional help or supervision from the family or a supportive adult. These data can also be valuable teaching tools to demonstrate the effect of behaviors and diabetes care practices on glucose outcomes and can be used to encourage self adjustment and beneficial changes in behavior. When patients or parents record or report fabricated glucose data, the meter memory can be used to discover such behaviors, which are an alert to the need for psychological counseling. It should be emphasized that glucose meter memories and clinic downloads of the monitoring data are not substitutes for regular review at home of BG readings by the patient and his/ her family. It is important to teach children, adolescents, and their parents to use trends and patterns regardless of the clinical management tool they use.

Increasingly, these devices can be downloaded onto the family's home computer or the manufacturer's website for family review and for transmission electronically to the Diabetes Care Team when families require advice on management. This allows more frequent contact between the family and the Diabetes Care Team for electronic or phone consultation. As this may lead to improved diabetes management, diabetes teams will need to determine whether adjustments in staffing requirements are needed to accommodate the additional time necessary to utilize this new technology, and some mechanism to reimburse for these services is essential.

Mobile phone usage among adolescents is becoming nearly ubiquitous and a high proportion of adolescents own smartphones (phones with a mobile computing platform). There has also been a proliferation of applications (apps) for smartphones designed to enhance diabetes self-management. These include apps for tracking data (e.g., BG values, insulin doses, and carbohydrates), apps for teaching and training, food reference databases, and social blogs. Although mobile health (mHealth) apps have the potential to improve chronic disease care beyond the traditional outpatient healthcare provider–patient encounter, there currently is a lack of evidence regarding their clinical effectiveness. It should also be appreciated that there are challenges such as lack of integration with the healthcare delivery system and potential threats to safety and privacy (21).

Nutrition

Nutrition is discussed elsewhere, but in general, the entire family should consume the same balanced diet recommended for the child with diabetes. Provided the family had a healthful diet before diagnosis, the

child can continue to follow the family's diet. The family should be taught how to handle food at festive occasions (small portion size of calorie dense foods, insulin dose changes, encourage activity) rather than avoid attending celebrations.

Exercise

The child/ adolescent should be encouraged to participate fully in physical activities, and must be taught when to consume an extra snack and/or reduce the dose of insulin based on BG testing. This is important to reinforce especially in families where girls are not allowed much physical activity, and if diabetes is perceived as a disease (the 'ill' child should not be 'tired out'). If hypoglycemia has occurred during activity, intensive education may be needed to overcome the fear of future hypoglycemia.

Transition to adult care

The developmental stage from the late teens through the twenties, referred to as emerging adulthood, is an especially challenging time for patients with T1DM, a period of life typified by competing educational, social, and economic priorities. The process of transition from pediatric to adult care is challenging for many youth. Numerous reports from centers in different countries, including those with universal health insurance systems, show that between 25 and 65% of young adults receive no medical follow-up; i.e., experience gaps between pediatric and adult diabetes care for significant periods of time (4, 22–28), decreased post-transition clinic attendance (5, 25, 26, 29), and patient dissatisfaction with the transition experience (25, 26, 30). Adverse diabetes-related outcomes, including poor glycemic control (31), increased post-transition diabetes-related hospitalizations (23–26, 28), emergence of chronic diabetes complications (6, 22, 28, 32–34), and premature mortality (6, 33, 35), have been reported in emerging adults.

To insure continued high-quality medical care, the transition process should be a planned, purposeful movement from a child-centered to adult-oriented healthcare system (36). A recent position statement from the American Diabetes Association, however, acknowledges the dearth of empirical evidence; therefore, recommendations are based on expert opinion and generally are not informed by high-quality clinical studies (37).

The age of transfer to an adult clinic varies by location and healthcare delivery system, and is influenced by local practices and resources, patient and family preferences, and national policies (26, 28, 38).

There are no empirical data to recommend an optimal age for transition to occur. A recent US

study of high school youth showed that those who had transferred to adult care before their final year of high school (i.e., at an earlier age) had worse glycemic control 1 yr after graduating from high school as compared with youth who remained in the pediatric healthcare system (and did not experience declines in glycemic control) (39). These observations suggest that early transition from the pediatric to the adult healthcare system may be associated with worse glycemic control (39).

Discussion about transition to another care team or diabetes care provider at several visits before transition occurs helps young people prepare for transition. In addition, providing counseling on how care and practices may differ in adult clinics may be helpful to teens (40).

Studies show that physician continuity and care coordination can help improve transition to adult care (27, 41). A planned, structured transition to adult diabetes care is expected to improve outcomes and helps to ensure continuity of care (42) and organized transition services may decrease the rate of loss to follow-up (27, 43).

Programs featuring transition coordinators or 'patient navigators' decrease post-transition gaps and improve post-transition clinic attendance and reduce DKA rates (43). The diabetes nurse has the potential to play a coordinating role to bridge the gap between pediatric and adult care (44).

Joint attendance of pediatric and adult diabetes care providers at the last pediatric clinic visit and first adult clinic appointment may be beneficial (41, 45).

Alternatively, a combined adolescent/young adult clinic with both pediatric and adult diabetes specialists has been proposed as an optimal model of transition to adult care (46, 47).

Further data are needed on best practices for transition of care. However, continued regular contact with a Diabetes Care Team is essential for late teens/young adults.

Barriers to care

There are many potential barriers to optimal diabetes care. These include financial burdens, psychosocial instability including broken homes, poor adjustment to the diagnosis, detrimental health beliefs, limited or inconsistent access to insulin, food, supplies, and care. In addition to personal challenges, great disparities exist in the level of pediatric diabetes care available to children, resulting from a wide range of factors across the world, from huge imbalances of geographic, economic, and scientific development to gender discrimination. Disparities are most apparent between well-educated majority populations and less educated, poorer, racial–ethnic minority subgroups.

Care for minority children and children of recent immigrants

Globalization and migration are great challenges to the healthcare systems of the developed as well as the developing world. With the urbanization movement in emerging countries, many children and their parents become newcomers in cities, or leave home alone with extended family members.

Barriers to treatment that affect the care of minority children as well as children of recent immigrants may be unfamiliar to the diabetes team and will negatively impact diabetes care in these children. Recognition of these barriers is necessary to optimize care, and novel ways to overcome these unfamiliar cultural barriers requires cooperation, communication, and the establishment of trust among all team and family members. Moreover, the perceived and, sometimes, actual access to healthcare by immigrant and minority families may be different than that of the country's majority inhabitants. Awareness of these perceptions and differences requires cultural sensitivity, careful inquiry, and knowledge of the family's social circumstances. Proper care requires not only attention to usual medical needs but also attention to the varying and unique need for support required by minority and immigrant families to access and optimally utilize medical care.

- Licensed interpreters must be used when needed. If a licensed interpreter is not available, a non-family member may serve as an interpreter. The child or other family member should only be used as an interpreter if no other option is available.
- Use of culturally sensitive tool boxes can aid in communication, counseling, diet advice, and encouraging empowerment and for altering preconceptions or negative and unhealthful beliefs about diabetes. An example of such materials is EthnoMed (www.ethnomed.org)
- Assistance in accessing care is an essential part of comprehensive diabetes care. Travel to clinics can be extremely challenging for children in rural communities, especially during emergencies. It is very important to establish regional pediatric diabetes care centers to facilitate the implementation of standard diabetes care.
- Dietary patterns of migrant families may be very different and must be understood for effective dietary advice to be given. For example, south Asians have high carbohydrate diets, and many are vegetarians; conversely, communities originating in coastal areas may typically eat large amounts of sea food.
- Knowledge of a family's cultural and religious beliefs can be critical to providing care, e.g., fear of contagion, diminished job and marriage

prospects, and the stigma of a chronic disease may delay or prevent the family from providing urgent or necessary daily diabetes treatment (33). Such stigmatization may result in the family keeping diabetes a secret, which may prevent the child with diabetes from eating and/or taking insulin at the appropriate times, or force him/her to eat inappropriately, leading to hypoglycemia or ketosis. Moreover, this can also prevent adequate care being provided by teachers/classmates/colleagues in the event of emergencies such as hypoglycemia. Encouraging the family to inform at least a few critical persons such as the child's teacher or a close friend may be crucial for getting help in such circumstances. In addition, giving awareness talks in the schools attended by affected children may considerably reduce stigmatization. In some regions, female patients might not receive appropriate diagnosis and treatment due to gender discrimination.

- Diabetes may be a deterrent to education and job prospects. In some countries, diabetes makes the person ineligible for several government jobs. Educational institutions, especially with residential requirements, have been known to refuse admission to applicants with diabetes. This may translate into even further, lifelong, dependence on family for covering health costs. It is particularly important for the family to be encouraged to educate the child and improve future earning capacity, to ensure continuing treatment is affordable during adulthood. The Diabetes Care Team should also be alert to instances of such discrimination, and may be able to prevent it. Getting societal and political support can be crucial to challenge instances of discrimination, whether by diabetes professionals, support groups, or both working together.

Attention to literacy and numeracy (of parents and child)

Deficiencies in literacy and numeracy can make diabetes education and management very difficult. Even relatively simple tasks such as reading and recording BG values and insulin doses may be difficult. Pictorial materials can be developed to cope with these situations. Innovative measures can be used, such as teaching the mother or child to draw the numbers because they cannot write them, providing premarked syringes (wrapped with colored tape to mark the dose), and using color coding to designate doses of insulin based on proximity of glucose reading to target range. Somewhat similar is the problem of multiple languages or dialects: educational and instructional materials may not be available in the local language.

Quality of care, structure of care, processes of care and outcomes

Diabetes care centers need methods to evaluate the quality of the diabetes services they provide and the outcomes of their management. Improvements in processes of care generally precede improvements in clinical outcomes. The impact of changes in the structure of care on clinical outcomes is less well studied in pediatric diabetes.

Tracking relevant outcomes is essential to the quality improvement process. For example, the establishment of a system for benchmarking of diabetes treatment in Norway resulted in significant improvements associated with changes in management and the quality of screening assessments. Benchmarking combined with organized quality meetings and discussions improved diabetes outcomes (lower HbA1c levels and decreased frequency of severe hypoglycemia) on a national level (7). Quality improvement programs can result in improved adherence to recommended processes of care such as frequency of HbA1c determinations, ophthalmological, and urinary albumin excretion screening (34). Adherence to recommended guidelines for albumin excretion screening leads to earlier detection of abnormal albumin excretion; treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy has been shown to reverse this abnormality with anticipated decrease in risk of nephropathy (35, 36). Likewise, recognition of early background retinopathy offers the opportunity to intensify and improve glycemic control, which would be expected to decrease the rate of progression to proliferative retinopathy (37, 38). Regular ophthalmological screening may also identify those requiring urgent ophthalmologic treatment to prevent vision loss. The impact of quality improvement programs on HbA1c levels is less clear. Open benchmark reporting of outcome data from all pediatric diabetes centers, as has been done in Sweden over the past 10 yr, can identify best practices between centers and lead to improved glycemic control (39, 48, 49).

Although the level of glycemic control required to optimally decrease the risk of long-term complications is generally accepted to be an HbA1c of 7–8%, (53–64 mmol/mol). The multicenter Hvidore study has shown that most centers are unable to achieve a mean HbA1c of $\leq 7.5\%$ (58 mmol/mol) in the majority of children, especially in adolescents (40). This observation has recently been confirmed among participants in the SEARCH for Diabetes in Youth Study and the T1D Exchange Registry in the USA (50, 51). A lower HbA1c achieved by getting frequent hypoglycemic episodes may not be desirable; thus, the level has to be seen in conjunction with the SMBG logs. In situations where the HbA1c and SMBG logs are

significantly mismatched and the SMBG is accurate, a hemoglobinopathy or other conditions affecting HbA1c should be suspected.

Necessary quality ‘benchmark’ information, must be collected from paper or computer records and analyzed at 3–12 month intervals, to determine improvement or deterioration over time. Standardized clinic data sheets, registries and databases all facilitate these efforts. Adequate data management and statistical analysis capabilities are required to analyze outcome data for quality improvement assessment. Table 1 gives examples of indicators of both processes of care and clinical outcomes important to pediatric diabetes services (41).

Markers of structure of care include the following:

- Composition of the Diabetes Care Team.
- Facility available to the team and patients, including resources and space for patient care and education.
- Access to care (availability for phone consultation 24 h/d, 7 d/wk).
- Performance and documentation of initial and ongoing diabetes education following current guidelines.

Comparisons of individual center results are an important part of quality improvement. Individual centers can compare their outcomes (e.g., monthly or annual reports) with published guidelines or other pediatric diabetes centers. Consortia of diabetes centers or study groups that have agreed to collect and publish longitudinal data, such as the Hvidore Study Group, the German and Austrian Diabetes Quality Control Initiative (DPV), the SWEET study, the UK Clinical Registry, the US SEARCH for Diabetes in Youth study group, and the T1D Exchange, have provided helpful outcome data from multiple pediatric diabetes centers (7, 13, 29, 50–55).

Individual center results have also been published, but consistent longitudinal data from individual centers are less available than those of study groups.

Multicenter studies have published analyses of some processes of care that may affect outcomes, but additional studies are needed to fully define best care practices. However, these datasets will allow pediatric Diabetes Care Teams to identify some processes of care that result in improvement in biological outcomes, improving quality of care for children throughout the world.

Care of children in other settings

Children with diabetes in the school setting

Children spend 40–50% of their waking hours in school. Diabetes care in school is an important part

Table 1. Examples of quality indicators reflecting the process and outcomes of diabetes care, relevant for pediatric diabetes. Adapted from (41)

Goal	Quality indicator
Normal growth	Percentage of patients with height >3rd percentile [adjusted for mid-parental height (MPH)]
Normal physical development	Average BMI in diabetic children compared with non-diabetic children
Normal pubertal development	Percentage of patients with BMI >10th and <85th percentile Mean age at menarche in girls
Glycemic control	Mean HbA1c achieved in all patients and by age group
Low rate of acute complications	Frequency of severe hypoglycemia in all patients and by age group Frequency of admission because of diabetic ketoacidosis after onset of diabetes
Prevention of microvascular complications	Percentage of patients with eye exams during the past year Percentage of patients with urine albumin extraction rate determined during the past year Percentage of patients beyond 5 yr of diabetes with diabetic retinopathy Percentage of patients beyond 5 yr of diabetes with diabetic nephropathy Percentage of patients with persistent microalbuminuria receiving angiotensin-converting enzyme inhibitors (or other interventions for microalbuminuria)
Prevention of cardiovascular complications	Percentage of patients with lipid levels available during the past year Percentage of patients with blood pressure recordings available during the past year Percentage of patients with hypertension Percentage of patients with hyperlipidemia Percentage of patients with hypertension receiving antihypertensive therapy Percentage of patients with dyslipidemia receiving lipid-lowering therapy
Intensive therapy	Percentage of patients on flexible insulin regimen Percentage of patients on insulin pumps Frequency of glucose monitoring
Multidisciplinary care	Percentage of patient who have met with nutritionist during the past year Percentage of patient who have met with diabetes educator in past year Percentage of patient who have had psychosocial assessment in past year
Optimal social adjustment	Average number of days spent in hospital Average number of days where school was missed because of diabetes QoL in patients with diabetes QoL in parents of patients with diabetes Percentage of missed appointments
Number of visits annually	Percentage of patients with ≥3 ambulatory visits annually Number of visits per patients per year and mean and median number of visits per patient per year

BMI, body mass index; HbA1c, hemoglobin A1c; QoL, quality of life.

of their diabetes management plan. The school should make provisions for the child to keep/carry meter and insulin and a place where testing and injecting can be done (e.g., class room itself, medical room, etc.). It should not alter a child's prescribed medical treatment, but changes in activity patterns should be incorporated into the medical plan (e.g., extra snacks for extra activity). The child has the right to participate equally in all school activities, including outdoor activities and sponsored events away from school, and to receive adult support for diabetes care during school hours (E). At the same time, school staff should not allow the child to use diabetes as an excuse to manipulate situations.

- School personnel must be trained to provide or supervise care prescribed by the diabetes team. This includes access to food in case of potential

hypoglycemia (e.g., unusual play or physical activity), insulin dose verification and administration by injection or as a bolus with an insulin pump. The staff should be aware of factors that affect glucose levels, such as food intake and physical activity, and assist in insulin dose decisions or have a plan to communicate with parents as necessary. They must be provided contact numbers of parents and the health team for assistance in decision-making or emergencies.

- School personnel must be supportive of providing diabetes care and encouraging diabetes management during school hours.
- Testing BG in young children and older newly diagnosed children and adolescents until they are capable of performing the task independently. If CGM is used, school personnel should receive training and specific instructions about how to

respond to sensor data and when it is necessary to perform a BG measurement.

- Identification and treatment for all degrees of hypoglycemia. Although most teens are fairly independent with diabetes management at school, nonetheless, they may require assistance with management of moderate to severe hypoglycemia. A recent communication by members of ISPAD, the majority felt it was appropriate for school staff to administer glucagon in the event of emergencies (personal communications). Therefore, all school personnel should be trained to recognize hypoglycemia symptoms, initiate treatment, and when to call for assistance or how to treat severe hypoglycemia. A recent study showed that 75% of children in school experienced an episode of hypoglycemia requiring assistance from school personnel with a median number of five hypoglycemic episodes during one school year (42). Newer, easier to use formulations of glucagon are in development and should facilitate glucagon administration at home or school.

Most national diabetes associations and organizations provide published guidelines for school care and recommendations and programs to assist school personnel and families to coordinate diabetes care in schools (43, 44). These resources are available on websites, or as a DVD or in print. Examples are the American Diabetes Association, Safe at School program, with educational slide presentations designed especially for school personnel, (www.diabetes.org/schooltraining), and the Australian Diabetes Council 'Management of Diabetes in School' (www.diabeteskidsandteens.com.au/teachers_and_schools). However, reports indicate that while school personnel can become knowledgeable about the complex medical care requirements of children with diabetes, many remain apprehensive about taking on the responsibility of providing diabetes care (45, 56).

Children with diabetes in organized camps

Many local and national diabetes organizations manage residential and day summer camps for children with diabetes, and it is estimated that worldwide, 15 000–20 000 children annually attend diabetes camps (46). Diabetes camps are usually staffed by professionals and volunteers trained in the management of children with diabetes. Diabetes camps offer children and adolescents the opportunity to enjoy a camping experience in a safe environment and to experience a setting where caring for diabetes is a shared experience with other campers who also have diabetes. For many children, this is an opportunity to meet other children with diabetes and learn healthy ways to manage diabetes

(47–51). During their diabetes camp experience, many children learn more about how to care for their diabetes and may subsequently be able to safely attend any camp of their choosing or enjoy a safe camping experience with their family. Certified camps specializing in the care of children with diabetes can be found on the Internet.

Many national organizations have position statements or guidelines for the care of children with diabetes in a camp setting. These are valuable references and should be reviewed by camp medical directors to ensure adherence to national standards (46).

Camps specializing in children with diabetes should have:

- Adequate staff trained to manage children with diabetes.
- Available insulin to meet the needs of the children.
- Knowledge of insulin dose adjustments for the increased levels of activity that are usual at camps.
- An understanding of how to adjust settings and maintain insulin pumps if they are used at the camp.
- The ability to test BG, urine or blood ketones, and have adequate facilities to manage emergencies.
- All staff trained to recognize and treat hypoglycemia.
- Medical staff trained to identify and treat early ketosis and when referral to a medical facility should be initiated.
- At least one staff member with knowledge of medical nutrition therapy, carbohydrate content of meals, and the principles of adjusting insulin doses for variable carbohydrate content of meals.
- A plan to maintain a log of each camper's BG levels and insulin doses. It is usual practice to provide a parent or guardian with a copy of this log at the end of camp.

Most camps provide some education in diabetes management either in planned, formal sessions or, more commonly, by taking advantage of helping campers 'learn by doing' and of 'teachable moments' to discuss one-on-one or in a group issues related to diabetes care and outcomes. Camp staff should understand, however, that the primary goal of camp is to provide an enjoyable recreational experience for each child and to interact with other children with diabetes in a safe environment (57, 58).

Other out of clinic activities in which the diabetes team may be involved includes the following:

- Local (and national) support groups.
- Advanced education sessions (e.g., advanced insulin pump classes, use of CGM).
- Resources (information leaflets/books, equipment, informational websites, etc.).
- Nutritional games/experiments/innovations.

- Discussion groups, activity days, visits, lectures, holiday events, camps, etc.

Cost of care and cost benefit analysis

Analysis of costs of care is important in helping to determine appropriate recommendations for care and in health policy decision-making (59). Clearcut data are limited, but it should be obvious that regular home BG monitoring is cost-effective, as even care in an emergency department or a short hospital admission for hypoglycemia or ketoacidosis would exceed the cost of several weeks of home BG and blood ketone testing (60). Most studies are small and do not include long-term cost-effectiveness (61, 62). Moreover, safe intensive diabetes management aimed at near-normal glycemia is impossible without frequent BG monitoring. The cost of diabetes care has increased dramatically in the past 10 yr with the introduction of analog insulins, increased use of insulin pumps, and increased frequency of BG testing. As continuous glucose sensor technology use increases, this will also add to the cost of care. Personal expenses for diabetes care vary widely around the world with costs being prohibitive in some countries and completely paid for by the state or private health insurance in others. Regardless of the source of payment for care, information about cost-effectiveness is required to inform healthcare decisions.

Countries and healthcare systems are adapting differently to the increased cost of diabetes care. Some countries or health insurance systems are considering or have already restricted use of newer insulin analogs and newer technologies requiring those choosing these technologies to bear up to 100% of the cost.

- Currently, analog insulins (both rapid- and long-acting) are 1.3–8 times as expensive as recombinant human regular and NPH insulin. However, both rapid- and long-acting analogs have been shown to reduce the frequency of mild and moderate hypoglycemia. The short-term costs need to be assessed to determine if the long-term benefit results in lower lifetime costs, taking QoL, long-term complications, and life expectancy into account.
- Limited available information does allow some assessment of the outcome of current insulin analog regimens using intermittent capillary BG monitoring in an affluent society with calculation of a projected cost:benefit ratio over the lifetime of an adolescent (52, 53).
- These reports suggest that basal–bolus therapy and, more recently, insulin pump therapy produce better long-term outcomes with a beneficial overall lifetime cost [weighing lifetime injection therapy using a multiple daily injection (MDI) regimen with NPH

as the basal insulin vs. insulin pump therapy] (54, 55).

- Studies are in progress to attempt to assess the benefit of continuous glucose monitoring, leading to studies using closed loop systems to improve health outcomes in youth with diabetes (56). Data are emerging rapidly on the use of such early forms of closed loop systems as low glucose suspend in children, and implementation of more fully closed loop systems (63–67).

Overall analysis of diabetes healthcare costs and utilization

It has been well documented that in adults, diabetes imposes a large economic burden (57); however, there is very little information on the cost of diabetes in children and adolescents, especially for those with type 2 diabetes (see chapter Type 2 diabetes in the child and adolescents). Yet such information is critical when assessing the economic burden of disease and evaluating the economic efficiency of diabetes prevention and control programs in this population. A recent population-based study conducted in Sweden reported that compared with the non-diabetic population, the direct medical cost for children with T1DM aged 0–14 yr was 7.7 times higher. These costs included healthcare expenditure in primary healthcare, outpatient and inpatient care, and prescribed drugs. The additional cost per person with diabetes in children was 3930 Euros (58). Additional data on cost of diabetes care in children with both T1DM and T2DM and cost-effective approaches to care are needed. In addition, data on the effect of different care models and practices on long-term outcomes are lacking. These data are essential to appropriate decisions in healthcare policy. In conclusion, as interventions to prevent long-term complications will reduce future healthcare expenditures and improve well-being; therefore, whenever possible, children with diabetes should be offered the most effective currently available care.

Conflicts of interest

The authors have declared no conflicts of interest.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Insulin treatment in children and adolescents with diabetes

Danne T, Bangstad H-J, Deeb L, Jarosz-Chobot P, Mungaie L, Saboo B, Urakami T, Battelino T, Hanas R. Insulin treatment in children and adolescents with diabetes.

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Executive summary and Recommendations

- Insulin treatment must be started as soon as possible after diagnosis (usually within 6 h if ketonuria is present) to prevent metabolic decompensation and diabetic ketoacidosis (A).
- In all age groups, as close to physiological insulin replacement as possible and optimal glycaemic control must be the aim (A). If available, an intensive insulin regimen is preferable [with analogs or regular/neutral protamine Hagedorn (NPH) insulin] (B). Although no insulin injection regimen satisfactorily mimics normal physiology, premixed insulins are not recommended for pediatric use (C). When insulin is provided through a help organization, the recommendation should be to provide regular and NPH as separate insulins, not premixed (E).

- Whatever insulin regimen is chosen, it must be supported by comprehensive education appropriate for the age, maturity, and individual needs of the child and family (A).
- Aim for appropriate insulin levels throughout 24 h to cover basal requirements and higher levels of insulin in an attempt to match the glycaemic effect of meals (E).
- Daily insulin dosage varies greatly between individuals and changes over time. It therefore requires regular review and reassessment (E).
- The distribution of insulin dose across the day shows great individual variation. Regardless of mode of insulin therapy, doses should be adapted to the circadian variation based on the daily pattern of blood glucose (B).
- Improvements in glycaemic control, particularly when provided by intensive insulin treatment with

multiple daily injection (MDI) or pump therapy with dose adjustments, reduces the risks of vascular complications. There is no reason to believe that this is not the case also in younger children (A, E).

- All children should have rapid-acting or regular insulin available for crisis management (E).
- It is essential that a small supply of spare insulin should be readily available to all children and adolescents so that the supply is uninterrupted (A).
- Children and adolescents should be encouraged to inject consistently within the same site (abdomen, thigh, buttocks, and arm) at a particular time in the day, but must avoid injecting repeatedly into the same spot to prevent lipohypertrophy (B).
- Insulins need to be administered by insulin syringes (or other injection devices) calibrated to the concentration of insulin being used (E).
- Regular checking of injection sites, injection technique, and skills remains the responsibility of parents, care providers, and health professionals (E).
- The use of pumps requires special education for users, but does not need to be restricted to centers with 24 h access to pump expertise. The pump user or the family should be taught how to switch to multiple injections with pens or syringes in case of emergency (E).
- Health care professionals have the responsibility to advise parents, other care providers, and young people on adjusting insulin therapy safely and effectively. This training requires regular review, reassessment, and reinforcement (E).

Introduction

Since the last guidelines were published in 2009 (1) the changes have been modest with respect to insulin treatment, but the different modes have been refined especially when it comes to insulin pump treatment (continuous subcutaneous insulin infusion, CSII). Overall there has been a paradigm shift toward MDI and CSII over the last decade. While previously therapies have focused on avoiding painful injections in children, leading to regimens with little flexibility and dietary restrictions, nowadays intensive regimens with differential substitution of basal and prandial insulin are becoming the gold standard also in pediatric diabetology. As CSII has been proven to be safe in all ages and allows exact and flexible insulin dosing in small increments, multiple bolus dosing without need for injections, different prandial bolus options, and hourly adaptation of basal insulin, this form of therapy has become the insulin regimen of choice in many places particularly for the very young. However, there is wide variation in insulin regimens, both within regions as well as between pediatric diabetologists in the same country that are not related to inadequate funding

of modern insulins or devices by national health care systems or insurance companies. Much of the variation can be explained by personal preference and experience of the respective diabetes team. As outcome comparisons through benchmarking and registries are implemented more widely in pediatric diabetes hopefully more guidance of regimens associated with better long-term prognosis becomes available.

Insulin therapy started in 1922 using regular insulin before each main meal and one injection in the night, usually at 1:00 hour. With the development of intermediate- and long-acting insulin, most patients moved to one or two injections per day after 1935. Already in 1960 a study showed that patients who were diagnosed between 1935 and 1945 and using one or two injections per day had a much higher risk of retinopathy after 15 yr of diabetes compared with those diagnosed before 1935 using MDIs (61 vs. 9%) (2).

There are no randomized controlled studies comparing the longer term outcomes of using older more traditional insulins with newer regimens when both groups receive equal educational input. But the fact that the traditional insulins have certain clinical limitations, has led to the development of new analogs, rapid- and long-acting. These insulins represent some improvement in the care of diabetes, but the extent in a clinical long-term setting is not fully established.

Adult data is not readily transferable to pediatric patients of different age groups (3), but in children and adolescents, as in adults (4), rapid-acting insulin (aspart) is rapidly absorbed and eliminated (5). Higher maximum insulin concentrations in adolescents vs. children were reported both for insulin aspart and human regular insulin (6), but not with glulisine (7). The results from reference (6) are in line with the relatively impaired insulin sensitivity and higher insulin concentrations reported in healthy adolescents (8, 9). Such findings highlight the necessity to study the effects of these new insulins in all age groups separately. The different rapid-acting analogs have different chemical properties, but no significant clinical difference in time of action and duration has been reported (10–12). Their advantages compared with regular (soluble) insulin are still under debate. The Cochrane review from 2006 (3) stated that in patients with type 1 diabetes, the weighted mean difference (WMD) of haemoglobin A1c (HbA1c) was -0.1% in favor of insulin analog (-0.2% when using CSII). In children and adolescents, blood glucose control has not been shown to be significantly improved with these analogs (13–17).

A reduction in hypoglycemia has been reported, both for lispro (14, 15, 18, 19) and aspart (20, 21). In the Cochrane review, the WMD of the overall mean hypoglycemic episodes per patient per month

was -0.2 [95% confidence interval (CI): $-1.1-0.7$] (3) in favor of rapid-acting insulin analogs. In adolescents, a significantly reduced rate was found with analogs (17), but in prepubertal children, no difference was found (14, 16). In the included pediatric studies, there was no difference found in prepubertal children (13, 14) or adolescents (17).

The basal insulin analogs have different modes of action. Insulin glargine is a clear insulin which precipitates *in situ* after injection whereas insulin detemir is acylated insulin bound to albumin. These analogs have reduced day-to-day variability in absorption compared with NPH-insulin, with detemir having the lowest within-subject variability (22, 23). So far the reduction in hypoglycemia and not in HbA1c is the most prominent feature (24) [A], both for glargine (25–31) and detemir (32–35). Parental fear of severe hypoglycemia, especially during night time, is an impediment to achieving morning blood glucose control. Lower body mass index (z-score) has been reported for detemir (33).

In randomized trials, better blood glucose control has been obtained using MDIs and pumps compared with a twice daily treatment (36, 37). The Diabetes Control and Complications Trial (DCCT) proved convincingly that intensive insulin therapy including a heavy multidisciplinary approach concerning insulin dose adjustment, education in adolescents with multiple injections or pumps, resulted in a lower rate of long-term complications (37). Cognitive impairment 18 yr after the conclusion of the DCCT study was unrelated to the rate of hypoglycemia during intensive therapy (38, 39). Also, in a cross-sectional clinical setting HbA1c, hypoglycemia, and diabetic ketoacidosis were not associated with the number of injections per day in pediatric populations (40). A longitudinal Australian study showed a significant decrease in retinopathy and microalbuminuria and only a slight decrease in HbA1c (from 9.1 to 8.5%) during the years 1990–2009 when MDI/CSII increased from 17 to 88%. Both retinopathy and microalbuminuria were significantly associated with one to two injections per day (41).

Insulin pump therapy is at present the best way to imitate the physiological insulin profile. Insulin is infused subcutaneously at a preprogrammed basal rate and boluses are added to counterbalance the intake of carbohydrates. CSII has mostly been compared with MDI with NPH as the long-acting insulin (42–52). A reduction in hypoglycemia and improved blood glucose control has been reported. One randomized study has recently confirmed these findings when glargine was the basal insulin in use (53), although in a study with people naive to CSII or insulin glargine, glycemic control was no better with CSII therapy compared with glargine-based MDI therapy (54). Several studies

have compared the use of analogs and regular insulin in pumps (55, 15). Insulin pumps from the onset have been found to result in superior metabolic control when compared with one to two injections per day (36) but not to MDI (53). In this study, diabetes treatment satisfaction was higher with CSII. In children <6 yr of age, pumps enabled better long-term metabolic control and lowered the risk of severe hypoglycemia better than MDI, especially when initiated at diagnosis (56). Data from a large pediatric survey showed a low incidence of acute complications at a mean HbA1c-level of 8.0% (57). An international consensus on pediatric indications and instructions for use has been published (58). The most recent meta analysis of six pediatric randomized controlled trials with 165 patients showed a reduction of HbA1c by 0.24% with CSII compared with MDI (mostly using NPH as basal insulin) (59).

Unequivocal evidence for the benefit of MDI, the analogs, and CSII-treatment in children is lacking. Carefully structured randomized studies are needed. The fact that these modalities are more expensive than conventional treatment has been an obstacle to the implementation of the use of them in many countries. However, the DCCT was performed with regular and NPH insulins, which are widely available in most countries. This implies that ISPAD's new practical recommendations have to be applicable for the total diabetes community worldwide.

The DCCT study and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study confirmed that an improvement in long-term glucose control, as obtained with intensified insulin therapy including heavy support and education, can reduce the incidence of complications and delay the progression of existing complications in type 1 diabetes, also in pediatric patients (37, 60, 61). A rapidly increasing numbers of centers around the world are introducing the basal/bolus concept of intensive insulin treatment already from the onset of diabetes.

Continuous glucose monitoring (CGM), both in patients using pump and MDI (age 6–70), has shown to give improved HbA1c without increasing the number of severe hypoglycemia, but the decrease in HbA1c was lower in the group that used the sensor $<70\%$ of the time (62) and the emerging results from recent studies with 'closed loop systems' are promising (63–65).

Insulin availability

- Children and adolescents with type 1 diabetes are dependent on insulin for survival and should have access to adequate amounts of at least regular and NPH-insulin.

Table 1. Types of insulin preparations and suggested action profiles according to manufacturers

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Rapid-acting analogs (aspart, glulisine, and lispro)	0.15–0.35	1–3	3–5
Regular/soluble (short acting)	0.5–1	2–4	5–8
Intermediate acting Semilente (pork)	1–2	4–10	8–16
NPH	2–4	4–12	12–24
IZS Lente type	3–4	6–15	18–24
Basal long-acting analogs			
Glargine	2–4	None	24*
Detemir	1–2	6–12	20–24
Long-acting			
Degludec†	0.5–1.5	None	>24
Ultralente type	4–8	12–24	20–30

NPH, Neutral Protamine Hagedorn insulin; IZS, insulin zinc suspension.

All insulins used must be produced under ‘Good Manufacturing Practice/Good Laboratory Practice’ conditions.

*The duration of action may be shorter than 24 h (82).

†Not yet approved worldwide.

- ISPAD and IDF are working toward making insulin available for all children and adolescents with diabetes and promoting universal insulin labeling.

Insulin formulation and species

- Many formulations of insulin are available; most have some role in the management of type 1 diabetes (Table 1).
- Human insulin is worldwide in distribution and use, but in many countries these are being superseded by analogs.
- Porcine or bovine insulins may be cheaper, but are virtually unavailable and subject to minimal use across the globe. The production of zinc-containing insulins (Lente) has been stopped.

The time of action of most insulins is dose-dependent in that a smaller dose has a shorter duration of effect and earlier (66, 67) peak and there is some evidence that lispro (68) and aspart (69) have the same time of action irrespective of dose. The results of these studies are obtained from a relatively small number of adult subjects, and the results in children may result in different profiles of action.

Regular insulin (short acting)

Regular soluble insulin (usually identical to human insulin) is still used as an essential component of most daily replacement regimens in many parts of the world either combined with:

- intermediate-acting insulin in twice daily regimen; or
- as premeal bolus injections in basal-bolus regimens (given 20–30 min before meals) together with intermediate-acting insulin once or twice daily or a basal analog given once or twice daily.

Rapid-acting insulin analogs

Several novel insulin analogs have been developed. Three rapid-acting types are currently available for children (aspart, glulisine, and lispro). They have a rapid onset and shorter duration of action than regular insulin (see Table 1). No clinical significant differences have been found between the analogs in the pediatric population (70).

The rapid-acting analogs:

- can when necessary be given immediately before meals because there is evidence that the rapid action not only reduces postprandial hyperglycemia but nocturnal hypoglycemia may also be reduced (14, 15, 18, 19);
- can in exceptional cases be given after food when needed (e.g., infants and toddlers who are reluctant to eat) (71);
- give a quicker effect than regular insulin when treating hyperglycemia, with or without ketosis, including sick days;
- are most often used as prandial or snack boluses in combination with longer acting insulins (see basal bolus regimens); and
- are most often used in insulin pumps (57).

Ultra-rapid-acting insulin

Ultra rapid-acting insulins are intended to better match the time–action profile of prandial insulins to cover the rapid increase in insulin meals and may be particularly useful for pumps and ‘closed-loop’ approaches. Because human insulin and rapid-acting insulin analogs generally exist in solution as stable hexamers, the delay in absorption is largely accounted for by the time it takes for hexamers to dissociate into monomers and dimers. New formulations of excipients to modify the insulin hexamer complex resulting in

more rapid dissociation into dimers and monomers after s.c. injection are currently tested in clinical studies for human regular insulin (BIOD-090 to 123, Biondi, Danbury, CT, U.S.A.) and insulin aspart (Fiasp, NovoNordisk, Bagsvaerd, Denmark) (72).

Safety of insulin analogs

As insulin analogs are molecules with modified structure compared with human insulin, safety concerns have been raised due to changes in mitogenicity *in vitro* (73). In previous guidelines we have commented on the issue of a potential link between insulin analogs and cancer. A series of four highly controversial epidemiological papers in *Diabetologia* had indicated such possibility for glargine. In a new statement published online in May 2013 the European Medicines Agency (EMA) has concluded that insulin glargine-containing medicines (Lantus[®], Optisulin[®], Sanofi, Paris, France) for diabetes do not show an increased risk of cancer. The EMA also notes that there is no known mechanism by which insulin glargine would cause cancer and that a cancer risk has not been seen in laboratory studies (74). Presently, there are no safety concerns that would preclude the use of insulin analogs in the pediatric age group.

IV insulin

Regular and rapid-acting insulins are equally suited for i.v. therapy in the following crisis situations (75):

- Diabetic ketoacidosis.
- Control of diabetes during surgical procedures.

However, regular insulin is less expensive.

Intermediate-acting insulins

The action profiles of the isophane NPH insulins make them suitable for twice daily regimens, tailored basal substitution, and for pre-bed dosage in basal-bolus regimens. As they are in suspension adequate preinjection mixing has to be ensured. Nevertheless they are associated with greater interindividual and intraindividual variability compared with soluble basal insulins (76).

Basal insulin analogs

The currently available basal insulin analogs are glargine, detemir, and degludec.

They show a more predictable insulin effect with less day-to-day variation, compared with NPH insulin (76) and no significant clinical difference (in adult) between detemir and glargine has been found (77). In

most countries, the two basal analogs are not formally approved for children below the age of 2 yr – there is a report of successful use of glargine in children from <1 to 5 yr of age (78). Basal analogs are more expensive (approximately +50 to 100%).

Glargine

A review of pediatric studies in the past 6 yr of once daily insulin glargine found a comparable or small improvement in HbA1c but a reduced rate of hypoglycemia, and a greater treatment satisfaction in adolescents compared with conventional basal insulins (79). However, in a Finnish retrospective study no difference concerning hypoglycemia and HbA1c was observed when glargine was compared to NPH as basal insulins (80). A randomized controlled trial in 125 preschool children aged 2–6 yr using CGM confirmed that a single injection of glargine appears at least equally effective to NPH usually injected twice daily also in the very young age. Thus glargine received regulatory approval for this age group (81).

The effect of glargine lasted for up to 24 h in adults, however, a waning effect can be seen approximately 20 h after injection (82). Lack of an accumulation effect of glargine given on consecutive days has been shown in one study (83). Some children report a burning sensation when injecting glargine due to the acid pH (84). Recently the EMA issued a positive opinion recommending approval for the investigational compound LY2963016 (Abrasia (R)), a new insulin glargine biosimilar product, for the treatment of type 1 and type 2 diabetes. The new insulin glargine product from Eli Lilly and Company (Indianapolis, U.S.A.) and Boehringer (Ingelheim, Germany) is the first biosimilar insulin recommended for approval in the European Union (EU). No pediatric data is available yet. Also, U300 is a new formulation of insulin glargine that is expected to last up to 40h. Preliminary data are showing positive outcomes with U300 performing the same in controlling blood glucose as insulin glargine but with less hypoglycemia during the day and night. U300 is based on the glargine molecule but requires a smaller volume of subcutaneous injection and U300 demonstrates a flatter and longer PK/PD profile than that of insulin glargine. Again, no pediatric data is available yet.

Detemir

A study with detemir in adults found the time of action to be between 6 and 23 h when doses between 0.1 and 0.8 U/kg were given (85). In a pediatric study, 70% of the patients used detemir twice daily (33). In adults, studies with detemir have shown weight reduction or

less weight gain (35), which has been observed also in children and adolescents (33).

Detemir is characterized by a more reproducible pharmacokinetic profile than glargine in children and adolescents with type 1 diabetes (23) and in a multicentre study the risk of nocturnal, severe hypoglycemia was reduced compared with glargine (86).

Long-acting insulins

Degludec

Degludec is a novel ultra-long-acting analog developed by NovoNordisk. It forms soluble multihexamers after subcutaneous administration, which then slowly dissociate and result in a slow and stable release of degludec monomers into the circulation extending the action for more than 40 initial results in pediatric patients, indicating that the long-acting properties of degludec are preserved in this age group also (87). The ultra-long action profile of degludec should allow less stringent timing of basal insulin administration from day-to-day which may be of use in the erratic lifestyles encountered frequently in the adolescent population. Another feature of degludec is that it can be mixed with short-acting insulins without the risk of forming hybrid hexamers and erratic pharmacokinetics/dynamics. Currently it is only approved for adults as the pediatric regulatory trials are evaluated insulins.

PEGylated Lispro

LY2605541 is a novel long-acting insulin analog developed by Lilly, based on the polyethyleneglycol (PEG)-ylation principle. It has not yet received regulatory approval (88).

Ultralente

Ultralente™ (Eli Lilly) and Ultratard™ (NovoNordisk) insulins were designed to have a duration of more than 24 h to meet basal insulin requirements, and therefore could be used in basal-bolus injection regimens. Their action profile in children appears to be extremely variable (66), with dose accumulation effect. If available, basal insulin analogs are superior to traditional long-acting insulins.

Premixed insulin preparations

Premixed insulins (fixed ratio mixtures of premeal and basal insulins) are used in some countries particularly for prepubertal children on twice daily regimens. Although they reduce potential errors in drawing up insulin, they remove the flexibility offered by

separate adjustment of the two types. Such flexibility is especially useful for children with variable food intake. Recently, premixed insulins have also become available with rapid-acting analogs. Biphasic insulin aspart 30 (30% aspart and 70% aspart bound to NPH) given for three main meals combined with NPH at bedtime was equally efficient as premixed human insulin (70% NPH) given for morning and bedtime with regular insulin for lunch and dinner in adolescents (89).

- There is no clear evidence that premixed insulins in young children are less effective, but there some evidence of poorer metabolic control when used in adolescents (40).
- Premixed insulins with regular (or rapid acting):NPH in different ratios, e.g., 10:90, 15:85, 20:80, 25:75, 30:70, 40:60, and 50:50 are available in various countries from different manufacturers.
- Premixed insulins are suitable for use in pen injector devices.
- Premixed insulins may be useful to reduce the number of injections when compliance (or adherence) to the regimen is a problem.

Inhaled insulin

This new form of insulin therapy has been investigated in children above 12 yr of age as part of a study in adults, but was not approved for clinical use in children. The sale of inhaled insulin was discontinued in 2007. Afrezza® (MannKind, Valencia, CA, U.S.A.) is a ultra rapid-acting mealtime insulin therapy being developed for type 1 and type 2 diabetes mellitus. It is a drug-device combination product, consisting of insulin inhalation powder and an inhaler which has received a conditional approval for adults by the Food and Drug Administration (FDA). No pediatric data is published yet.

Insulin concentrations

The most widely available insulin concentration is 100 IU/mL (U100). Treatment with U40 (40 IU/mL), U50, or other concentrations such as U500 is also acceptable, subject to availability and special needs. Care must be taken to ensure that the same concentration is supplied each time new supplies are received. Very young children occasionally require insulin diluted with diluent obtained from the manufacturer, but special care is needed in dilution and drawing up the insulin into the syringe. Rapid-acting insulin can be diluted to U10 or U50 with sterile NPH diluent and stored for 1 month (90, 91) for use in pumps for infants or very young children. Switching children from U40 to U100 insulin may increase practical problems in drawing up insulin, but

has not shown a decline in glycemic control in a large pediatric cohort (92).

Storage of insulin

Regulatory requirements state that the labeled insulin product must retain at least 95% of its potency at expiry date (93). At room temperature (25°C, 77°F), insulin will lose <1.0% of its potency over 30 d. In contrast, insulin stored in a refrigerator will lose <0.1% of its potency over 30 d (93). Storage recommendations are more often based on regulatory requirements regarding sterility than loss of potency (93). The individual manufacturer's storage recommendations and expiry dates must be adhered to. These usually recommend that:

- Insulin must never be frozen.
- Direct sunlight or warming (in hot climates) damages insulin.
- Patients should not use insulin that has changed in appearance (clumping, frosting, precipitation, or discoloration).
- Unused insulin should be stored in a refrigerator (4–8°C).
- After first usage, an insulin vial should be discarded after 3 months if kept at 2–8°C or 4 wk if kept at room temperature. However, for some insulin preparations, manufacturers recommend only 10–14 d of use in room temperature.
- In hot climates where refrigeration is not available, cooling jars, earthenware pitcher (*matka*), (94) or a cool wet cloth around the insulin will help to preserve insulin activity.

In children on small doses of insulin, 3 mL cartridges instead of 10 mL vials should be chosen to avoid wasting of insulin.

Injection sites

The usual injection sites are:

- Abdomen (the preferred site when faster absorption is required and it may be less affected by muscle activity or exercise).
- Front of thigh/lateral thigh (the preferred site for slower absorption of longer acting insulins).
- The lateral upper quadrant of the buttocks (the whole upper quadrant is useful in small children).
- Lateral aspect of arm (in small children with little subcutaneous fat, intramuscular injection is more likely and it may cause unsightly bruising).
- Rotation of injection sites are important also within the same area of injection.
- Cleaning or disinfection of skin is not necessary unless hygiene is a real problem. Infection at injection sites is rare (95).

Problems with injections

Local hypersensitivity reactions to insulin injections are uncommon but when they do occur, formal identification of the insulin (or more rarely preservative) responsible may be possible with help from the manufacturers. A trial of an alternative insulin preparation may solve the problem. If true allergy is suspected, desensitization can be performed using protocols available from the manufacturers. Adding a small amount of corticosteroids to the insulin may help (96). Lipohypertrophy with the accumulation of fat in lumps underneath the skin are common in children (97). Lipoatrophy was said to be uncommon since the introduction of highly purified insulins and analogs (98). But a very recent report indicates that lipoatrophy is a growing problem in patients using insulin analogs and possibly mostly in patients on pumps (99, 100).

Painful injections are a common problem in children. Check angle, length of the needle, and depth of injection to ensure injections are not being given intramuscularly and that the needle is sharp. Reused needles can cause more pain (101). Indwelling catheters (Insufion[®], i-port[®]) can decrease injection pain (102).

Leakage of insulin is common and cannot be totally avoided. Encourage slower withdrawal of needle from skin, stretching of the skin after the needle is withdrawn, or pressure with clean finger over the injection site.

Bruising and bleeding are more common after intramuscular injection or tight squeezing of the skin. Use of thinner needles have shown significantly less bleeding at the injection site (103).

Bubbles in insulin should be removed whenever possible. If the bubble is not big enough to alter the dose of insulin it should not cause problems. When using insulin pens, air in the cartridge can cause drops of insulin appearing on the tip of the pen needle, if withdrawn too quickly (104).

Insulin absorption

Insulin activity profiles show substantial variability both day-to-day in the same individual and between individuals, particularly in children (6, 66). The onset, peak effect, and duration of action depend upon many factors which significantly affect the speed and consistency of absorption. Young people and care providers should know the factors which influence insulin absorption such as:

- Age (young children, less subcutaneous fat → faster absorption).
- Fat mass (large subcutaneous fat thickness (105), lipohypertrophy (106), also with rapid-acting analogs (107) → slower absorption).

- Dose of injection (larger dose → slower absorption (66))
- Site and depth of s.c. injection (abdomen faster than thigh (108); no good data exist on absorption from thigh vs. buttock).
- s.c. vs. i.m. injection (i.m. injection → faster absorption in thigh (109). Accidental i.m. injections can cause variable glucose control.
- Exercise (leg injection, leg exercise → faster absorption) (110).
- Insulin concentration, type, and formulation (lower concentration → faster absorption) (111).
- Ambient and body temperature (higher temperatures → faster absorption) (105).
- In general, the absorption speed of rapid-acting analogs is less affected by the above mentioned factors (112–114).
- There is no significant difference in the absorption of glargine from abdomen or thigh (115). Exercise does not influence glargine absorption (116). There is a risk of hypoglycemia if injecting glargine intramuscularly, particularly in young and lean individuals (117).

Note: Faster absorption usually results in shorter duration of action

Hyaluronidase may increase absorption speed, either added to insulin, or injected prior to inserting an insulin pump infusion set ('pre-administration') (118). Long-term effectivity and safety need to be established before this can be recommended for a pediatric population.

Insupad (R), (Insuline, Petach Tikva, Israel) is a device that warms an area $2 \times 4 \text{ cm}^2$ just prior to injection of bolus insulin. The device is resited daily. It has been shown to reduce the total daily insulin dose by 20%, and achieve a 75% reduction in hypoglycemic episode. The Insupatch (R) (Insuline, Peath Tkva, Israel) has been developed for insulin pump therapy and has an integral heating element that is activated when a bolus is delivered. The action of insulin aspart peaks at 73 min without heat and at 43 min with heat (119). With these new devices the insulin requirements are lower, and can achieve an earlier peak reducing area under curve (AUC) for glucose and also reduce the risk of hypoglycemia

Administration of insulin

Devices for insulin delivery

Insulin syringes. Syringes are available in a variety of sizes in different countries, ensuring accurate dose delivery, but it is desirable to have small syringes with 1 U per mark (e.g., 0.3 mL, 100 U/mL) available for small children.

Plastic fixed-needle syringes with small dead space are preferable to glass syringes.

Plastic fixed-needle syringes are designed for single use. However, many individuals with diabetes successfully reuse them without significant increase in risk of infection (120). Reuse should be discouraged if there is concern about hygiene or injection pain as they become blunted when reused (101).

Insulin syringes must have a measuring scale consistent with the insulin concentration (e.g., U100 syringes).

Syringes must never be shared with another person because of the risk of acquiring blood-borne infection [e.g., hepatitis and human immunodeficiency virus (HIV) infections].

It is advisable that all children and adolescents with diabetes should know how to administer insulin by syringe because other injection devices may malfunction.

Appropriate disposal procedures are mandatory. Specifically designed and labeled 'sharps containers' may be available from pharmacies and diabetes centers. Special needle clippers (e.g., Safeclip[®], Becton Dickinson, Franklin lakes, NJ, U.S.A.) may be available to remove the needle and make it unusable. Without a 'sharps container', syringes with needles removed may be stored and disposed of in opaque plastic containers or tins for garbage collection.

Pen injector devices. Pen injector devices containing insulin in prefilled cartridges have been designed to make injections easier and more flexible. They eliminate the need for drawing up from an insulin vial; the dose is dialed up on a scale and they may be particularly useful for insulin administration away from home, at school, or on holidays.

Special pen injection needles of small size (4–6 mm) and diameter are available and may cause less discomfort on injection (103). Pen injectors of various sizes and types are available from the pharmaceutical companies. Some pens can be set to half unit increments. Half-unit pens are particularly useful for dosing in young children and during the remission phase when small dosing increments may help to avoid hypoglycemia. A few pens have a memory for taken doses, which can be practical especially for teenagers. Availability is a problem in some countries and although pen injectors may improve convenience and flexibility, they are a more expensive method of administering insulin.

Pen injector devices are useful in children on multiple injection regimens or fixed mixtures of insulin, but are less acceptable when free mixing of insulins is used in a two- or three-dose regimen.

Needle length. The traditional needle length of 8–13 mm (27 G) has been replaced by thinner needles that are 4–8 mm long (30–32 G). There is no longer reason for needles longer than 6 mm (121). A two-finger pinch technique is recommended for all types of injections to ensure a strict subcutaneous injection, avoiding intramuscular injection (122).

With 4–6 mm needles, the injections can be given perpendicularly without lifting a skin fold but only if there is enough subcutaneous fat, which often is the case in pubertal girls (at least 8 mm as the skin layers often are compressed when injecting perpendicularly) (123). Lean boys, however, have a thinner subcutaneous fat layer, especially on the thigh (123, 124). When injecting into the buttocks, the subcutaneous fat layer is usually thick enough to inject without lifting a skin fold. There is a risk of intradermal injections if 4–6 mm needles are not fully inserted into the skin.

Subcutaneous indwelling catheters. Such catheters (e.g., Insufion®, Unomedical, Denmark, i-port®, Medtronic, Northridge, CA, U.S.A.) inserted using topical local anesthetic cream, may be useful to overcome problems with injection pain at the onset of diabetes (102). The use of indwelling catheters do not affect metabolic control negatively (125). In children with injection problems, HbA1c has been lowered by using Insufion (126). However, the use of a basal analog and a short- or rapid-acting insulin at the same injection time in an indwelling catheter is not advisable in case of possible interaction of the two insulins. Indwelling catheters should be replaced every 2–4 d to prevent scarring and a negative effect on insulin absorption (127, 128).

Automatic injection devices. Automatic injection devices are useful for children who have a fear of needles. Usually a loaded syringe is placed within the device, locked into place and inserted automatically into the skin by a spring-loaded system. The benefits of these devices are that the needle is hidden from view and the needle is inserted through the skin rapidly. Automatic injection devices for specific insulin injectors are available (129).

Jet injectors. High pressure jet injection of insulin into the s.c. tissue has been designed to avoid the use of needle injection. Jet injectors may have a role in cases of needle phobia. The use of jet injectors has resulted in metabolic control comparable both to conventional injections and CSII (130), but problems with jet injectors have included a variable depth of penetration, delayed pain, and bruising (131). In a recent study, the insulin absorption was enhanced and

the duration of the glucose lowering action was reduced when using aspart insulin with a jet injector (132).

Continuous subcutaneous insulin infusion. The use of external pumps is increasing and is proving to be acceptable and successful (42–44, 46–52, 57), even in young infants (48, 133). Randomized studies in the pre-school group have failed to show better glycemic control (42, 134).

The positive effects on glycemic control and hypoglycemia in non-randomized observational studies have probably been influenced by the patient selection in these studies, such as good compliance and/or poor metabolic control. Pump therapy has also been found effective in recurrent ketoacidosis (135, 136). This highlights the importance of individualizing the decision of the modality of therapy for every situation.

An insulin pump is an alternative to treatment with MDI (including basal analogs) if HbA1c is persistently above the individual goal, hypoglycemia is a major problem or quality of life needs be improved (137, 138).

Pump therapy is an option for many patients to improve treatment satisfaction. In a review of five pediatric studies comparing CSII vs. MDI, a majority of the patients and families chose to continue with CSII after the completion of the studies, even in studies where insulin pumps showed no objective benefit (139). A randomized study of CSII vs. MDI from the onset of diabetes in 7–17 yr olds also found a significant improvement in treatment satisfaction in spite of no difference in HbA1c (140).

Insulin pump use is increasing particularly in the younger age group during the recent years, as clinicians become more comfortable with this form of treatment. In countries with a high pump penetration centers are starting particularly their preschool children from diabetes onset with CSII. There has been circumstantial evidence that this is associated with a more rapid recovery of mothers from depressive symptoms associated with the diagnosis of a chronic disease in their child (141).

CSII is used as a more physiological insulin replacement therapy (133). The newer generation of ‘smart’ pumps that automatically calculate meal or correction boluses based on insulin-to-carbohydrate ratios and insulin sensitivity factors have shown some benefits, i.e., reduced glucose variability (142) and a higher percentage of post-meal glucose readings within target level (143).

Insulin pump treatment may be hazardous when education and adherence to therapy is inadequate, because of the smaller depot of subcutaneous insulin and the sudden rise in ketones when insulin supply is interrupted. Pump stops for 5 h in adult patients resulted in B-ketone (beta-hydroxybutyrate) levels of

approximately 1–1.5 mmol/L but not DKA. Results in children and adolescents seem to be similar (144). Short disconnection of the pump gives a blood glucose increment of ≈ 1 mg/dL, i.e., 1.5 mmol/L per 30 min (145).

The risk of DKA when using pumps comparing with MDI is unchanged in several studies (50, 146) and even lower in a recent long-term cohort study (147).

A literature review found an increased risk of DKA in pediatric pump patients in some studies (148). Data on national levels have shown both an unchanged (149) and an increased risk of DKA (150, 147).

Patients using insulin pumps, especially younger children, will benefit from being able to measure B-ketones.

The short interruption of insulin supply when changing infusion sets did not affect short-term glucose control. However, a 30-min interruption of basal insulin infusion resulted in significant glucose elevation; approximately 1 mg/dL for each minute basal insulin infusion was interrupted (i.e., 1.5 mmol/L per 30 min) (145). Patients must be instructed on treatment of hyperglycemia, giving insulin with a pen or syringe in case of suspected pump failure (hyperglycemia and elevated ketone levels).

Rapid-acting insulin analogs are used in most pumps, and a meta-analysis has shown a 0.26% lower HbA1c when comparing with human regular insulin (28). Regular insulin is less often used in pumps but works well if rapid-acting insulin is not available.

Longer use of the infusion site may yield a faster peak of insulin and a shorter duration of insulin effect (151, 152).

Of the three rapid-acting insulins in current use, there are considerably more trial data relating to the use of insulin aspart and insulin lispro than to the use of insulin glulisine. The more widespread use of insulins aspart and lispro is supported by CSII studies that have demonstrated higher rates of occlusion and symptomatic hypoglycemia with insulin glulisine than with either of the other rapid-acting analogs (153). Lower percentage of basal insulin and more than seven daily boluses are an option for better metabolic control when using pumps (57). Motivation appears to be a crucial factor for the long-term success of this form of therapy (154).

Sensor-augmented pump therapy and 'closed loop'. In the Juvenile Diabetes Research Foundation (JDRF) study a significant improvement in HbA1c using sensor-augmented pump (SAP) compared with self-monitoring of blood glucose, but only in adults in the intention-to-treat-analysis (155). However, in a *post hoc* analysis the improvement in HbA1c was seen also in the non-adults who used the CGM at least 6 d/wk. Many children and adolescents find it difficult

to wear the sensor continuously (156), which may have prevented an overall positive effect on metabolic control in the JDRF study. In another randomized trial, an improvement was only seen when the device was worn for more than 60% of the time (157). In the STAR 3 1-yr study, which included both children and adolescents, they were reported to achieve treatment satisfaction (158), reduced HbA1c (159), and glycemic variability (160). Which patients are likely to profit from sensor-augmented therapy needs to be studied further.

An automatic shut-off of the pump to prevent hypoglycemia when the sensor has fallen below a preset threshold and the patient does not respond to alarms has been used successfully in children and adolescents (161). There was no evidence that this temporary shut-off may lead to a increased risk for DKA.

Short-term experiments in adolescents with a closed loop system where the sensor glucose level regulates the insulin delivery in the pump have been published (65). In 2011, a closed loop system used during the night in children and adolescents showed reduced risk of hypoglycemia compared with standard pump treatment (162). In 2013, a closed loop system used in a youth camp setting showed less nocturnal hypoglycemia and tighter glucose control than with SAP (64). Meanwhile studies have been also published using these systems safely and effectively in studies with pediatric patients in a home setting (163, 164).

Injection technique

Injections by syringe are usually given into the deep subcutaneous tissue through a two-finger pinch of skin at a 45° angle. A 90° angle can be used if the s.c. fat is thick enough. Pen injector technique requires careful education including the need to ensure that no airlock or blockage forms in the needle. A wait of 15 s after pushing in the plunger helps to ensure complete expulsion of insulin through the needle (104).

Self injection. It should be emphasized that a proportion of people with diabetes have a severe long lasting dislike of injections which may influence their glycemic control. For these persons, an injection aid, i-port, Insuflon (126), or insulin pump therapy may improve compliance.

There is great individual variation in the appropriate age for children to self-inject (165). The appropriate age relates to developmental maturity rather than chronological age. Most children over the age of 10 yr either give their own injections or help with them (165). Younger children sharing injection responsibility with a parent or other care provider may help to prepare the device or help push the plunger and subsequently under supervision be able to perform

the whole task successfully. Self-injection is sometimes triggered by an external event such as overnight stay with a friend, school excursion, or diabetes camp. Parents or care providers should not expect that self-injection will automatically continue and should accept phases of non-injection with the need for help from another person. Younger children on multiple injection regimens may need help to inject in sites difficult to reach (e.g., buttocks) to avoid lipohypertrophy.

Self-mixing of insulin. When a mixture of two insulins is drawn up (e.g., regular mixed with NPH), it is most important that there is no contamination of one insulin with the other in the vials. To prevent this, the following principles apply. There is no uniformity of advice but most often it is taught that regular (clear insulin) is drawn up into the syringe before cloudy insulin (intermediate- or long-acting). Vials of cloudy insulin must always be gently rolled (not shaken) at least 10 times, preferably 20 times (166), to mix the insulin suspension before carefully drawing it up into the clear insulin. If the cloudy insulin is of Lente type the mixture must be administered immediately, otherwise the regular component interacts with zinc which blunts the action (167, 168). Insulins from different manufacturers should be used together with caution as there may be interaction between the buffering agents. Rapid-acting insulin analogs may be mixed in the same syringe as NPH immediately before injections (169, 170). Immediate injection of a mixture of Ultralente and Humalog has been found not to diminish the Humalog effect (171). The manufacturer recommends that glargine should not be mixed with any other insulin before injection, but there is some evidence that it can be mixed with insulin lispro and aspart without affecting the blood glucose lowering effect (172) or HbA1c (173). The manufacturer recommends that detemir should not be mixed with any other insulin before injection. There are no available studies on this.

Insulin regimens

The choice of insulin regimen will depend on many factors including: age, duration of diabetes, lifestyle (dietary patterns, exercise schedules, school, work commitments, etc.), targets of metabolic control, and particularly individual patient/family preferences.

- The basal-bolus concept (i.e., a pump or intermediate-acting/long-acting insulin/basal analog once or twice daily and rapid-acting or regular boluses with meals and snacks (174) has the best possibility of imitating the physiological insulin profile with dose adjustments.
- At least two injections of insulin per day (mixing short-acting/rapid-acting and basal insulin) are advisable in most children.

- Most regimens include a proportion of short- or rapid-acting insulin and intermediate-acting insulin or long-acting basal analog, but some children may during the partial remission phase maintain satisfactory metabolic control (i.e., an HbA1c close to the normal range) on intermediate- or long-acting insulins or alternatively prandial insulin without basal alone.

Principles of insulin therapy

Frequently used regimens

Basal-bolus regimen

- Of the total daily insulin requirements, 40–60% should be basal insulin, the rest pre-prandial rapid-acting or regular insulin.
- Injection of regular insulin 20–30 min before each main meal (breakfast, lunch, and the main evening meal).
- Intermediate-acting insulin or basal/long-acting analog at bedtime or twice daily (mornings and evenings).
- Injection of rapid-acting insulin analog immediately before (or in exceptional cases after) (14, 71) each main meal (breakfast, lunch, and main evening meal) adjusted to glycemia, meal content, and daily activity. Rapid-acting analogs may need to be given 15–20 min before the meal to have full effect, especially at breakfast (175, 176).
- Intermediate-acting insulin or basal/long-acting analog at bedtime, probably before breakfast and occasionally at lunchtime or twice daily (mornings, evenings, preferable with small doses <10–15 U that do not have a 24-h duration).

Pump therapy (CSII)

- Insulin pump regimes are gaining popularity with a fixed or variable basal rate and bolus doses with meals.

Sensor-augmented therapies

- CGM systems used together with CSII or MDI is well tolerated in children with diabetes, but the usage over time declined in studies (155, 177).

Less-intensive regimens

- Three injections daily using a mixture of short- or rapid- and intermediate-acting insulins before breakfast; rapid or regular insulin alone before afternoon snack or dinner/the main evening meal;

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intermediate-acting insulin before bed or variations of this.

- Two injections daily of a mixture of short- or rapid- and intermediate-acting insulins (before breakfast and dinner/the main evening meal).

Note: None of these regimens can be optimized without frequent assessment by self-monitored blood glucose (SMBG)

Daily insulin dosage

Dosage depends on many factors such as

- Age
- Weight
- Stage of puberty
- Duration and phase of diabetes
- State of injection sites
- Nutritional intake and distribution
- Exercise patterns
- Daily routine
- Results of blood glucose monitoring and glycated hemoglobin
- Intercurrent illness

Guideline on dosage

The 'correct' dose of insulin is that which achieves the best attainable glycemic control for an individual child or adolescent without causing obvious hypoglycemia problems, and the harmonious growth according to weight and height in children's charts.

- During the partial remission phase, the total daily insulin dose is often <0.5 IU/kg/d.
- Prepubertal children (outside the partial remission phase) usually require 0.7–1.0 IU/kg/d.
- During puberty, requirements may rise substantially above 1.2 IU/kg/d and even up to 2 IU/kg/d.

Distribution of insulin dose

Children on twice daily regimens often require more (around two thirds) of their total daily insulin in the morning and less (around one third) in the evening. On this regimen, approximately one third of each insulin dose may be short- or rapid-acting insulin and approximately two thirds may be intermediate-acting insulin although these ratios change with greater age and maturity of the young person.

On basal-bolus regimens the night-time intermediate-acting insulin may represent between 30% (typical for regular insulin) and 50% (typical for rapid-acting insulin) of total daily insulin. Approximately 50% as rapid-acting or approximately 70%

as regular insulin is divided up between three and four premeal boluses. When using rapid-acting insulin for premeal boluses, the proportion of basal insulin is usually higher, as short-acting regular insulin also provides some basal effect.

Glargine is often given once a day, but many children may need to be injected twice a day or combined with NPH to provide full daytime basal insulin coverage (29, 178). Glargine can be given before breakfast, before dinner, or at bedtime with equal effect, but nocturnal hypoglycemia occurs significantly less often after breakfast injection (82). When transferring to glargine as basal insulin, the total dose of basal insulin needs to be reduced by approximately 20% to avoid hypoglycemia (178). After that, the dose should be individually tailored.

Detemir is most commonly given twice daily in children (33). When transferring to detemir from NPH, the same doses can be used to start with, but be prepared to increase the detemir dose according to SMBG results.

Insulin dose adjustments

Soon after diagnosis

- Frequent advice by members of the diabetes team on how to make graduated alterations of insulin doses at this stage is of high educational value.
- Insulin adjustments should be made until target BG levels and target HbA1c are achieved.
- If frequent SMBG is not possible, urinary tests are useful, especially in the assessment of nocturnal control.

Later insulin adjustments

- On twice daily insulin regimens, insulin dosage adjustments are usually based on recognition of daily patterns of blood glucose levels over the whole day, or a number of days or in recognition of glycemic responses to food intake or energy expenditure.
- On basal-bolus regimens, flexible or dynamic adjustments of insulin are made before meals and in response to frequent SMBG. In addition, the daily blood glucose pattern should be taken into account. The rapid-acting analogs may require postprandial BG tests approximately 2 h after meals to assess their efficacy. Frequently, insulin is dosed based on food consumption (carbohydrates) and the current SMBG reading. Pumps have the possibility of delivering the bolus dose in different ways in order to reduce the postprandial blood glucose excursions (179). Many newer insulin pumps allow programming algorithms

(bolus guide) for these adjustments for current blood glucose and amount of carbohydrate intake.

- Downloading the blood glucose meter to a computer can help in discovering daily patterns in glucose levels.

Advice for persistent deviations of BG from target

- Elevated BG level before breakfast → increase pre-dinner or pre-bed intermediate- or long-acting insulin (BG tests during the night are needed to ensure that this change does not result in nocturnal hypoglycemia).
- Rise in BG level after a meal → increase premeal rapid/regular insulin.
- Elevated BG level before lunch/dinner meal → increase pre-breakfast basal insulin or increase dose of pre-breakfast regular/rapid-acting insulin if on basal-bolus regimen. When using rapid-acting insulin for basal-bolus regimen, the dose or type of basal insulin may need to be adjusted in this situation as the analog has most of its effect within 2–3 h after injection.
- When using carbohydrate counting, persistent elevations of postmeal BG may require adjustment in the insulin to carbohydrate ratio. The ‘500-rule’ is often used to obtain an initial ratio when starting with carbohydrate counting (divide 500 by the total daily dose – basal and bolus insulin – to find the amount of carbohydrates in grams that 1 U of insulin will cover).
- The insulin to carbohydrate ratio for an individual meal, for example, breakfast, can be calculated by dividing the carbohydrate content in grams by the insulin dose in units. This method often gives the most accurate results for an individual meal, and can preferably be used for breakfast when there usually is an increased insulin resistance. If the glucose before and after the meal differ more than 2–3 mmol/L (20–30 mg/dL), the correction factor (see below) can be used to calculate out how much more (or less) insulin should have been ideally given for a certain meal.
- Some centers also count protein and fat for calculating insulin requirements when using a pump [fat-protein units (FPUs)] (174). One FPU equals 100 kcal of fat or protein, and requires the same amount of insulin (as an extended bolus) as 10 g of carbohydrates.
- Correction doses (also called insulin sensitivity factor, correction factor) can be used according to the ‘1800 rule’, i.e., divide 1800 by total daily insulin dose to get the mg/dL that 1 U of rapid-acting insulin will lower the blood glucose. For

mmol/L, use the ‘100 rule’, i.e., divide 100 by total daily insulin dose (180). For regular insulin, a ‘1500 rule’ can be used for results in mg/dL and a ‘83-rule’ for results in mmol/L. However, correction doses should always be adjusted individually before administration, depending on other factors affecting insulin resistance like exercise.

- Rise in BG level after evening meal → increase pre-evening meal regular/rapid-acting insulin.

In addition

- Unexplained hypoglycemia requires re-evaluation of insulin therapy.
- Hyperglycemia or hypoglycemia occurring in the presence of intercurrent illness requires a knowledge of ‘sick day management’.
- Day-to-day insulin adjustments may be necessary for variations in lifestyle routines, especially exercise or dietary changes.
- Various levels of exercise require adjustment of diabetes management.
- Special advice may be helpful when there are changes of routines, travel, school outings, educational holidays/diabetes camps, or other activities which may require adjustment of insulin doses.
- During periods of regular change in consumption of food (e.g., Ramadan) the total amount of insulin should not be reduced but redistributed according to the amount and timing of carbohydrate intake. However, if total calorie intake is reduced during Ramadan, the daily amount of bolus insulin for meals usually needs to be reduced, for example, to two thirds or three quarters of the usual dose.

Dawn phenomenon

Blood glucose levels tend to rise in the hours of the morning (usually after 05:00 hours) prior to waking. This is called the dawn phenomenon. In non-diabetic individuals the mechanisms include increased nocturnal growth hormone secretion, increased resistance to insulin action, and increased hepatic glucose production. These mechanisms are more potent in puberty.

Pump studies (181–183) have shown that younger children often need more basal insulin before midnight than after (reversed dawn phenomenon). With a basal/bolus analog regimen this can be achieved by giving regular instead of rapid-acting insulin for the last bolus of the day (night time blood glucose levels need to be checked).

In individuals with type 1 diabetes, fasting hyperglycemia is predominantly caused by waning insulin levels, thus exaggerating the dawn phenomenon. Morning hyperglycemia can in some cases be preceded by nighttime hypoglycemia (so called Somogyi

phenomenon), being seen less often in pump therapy compared with MDI (184). Correction of fasting hyperglycemia is likely to require an adjustment of the insulin regimen to provide effective insulin levels throughout the night and the early morning by the use of:

- intermediate-acting insulin later in the evening or at bedtime a longer acting evening insulin/basal insulin analog, and
- change to insulin pump treatment.

Conflicts of interest

RH has received lecture honoraria from NovoNordisk, Lilly, Sanofi, Medtronic, Johnson & Johnson, and Roche. PJ-C has received lecture fees from Eli Lilly, Novo-Nordisk, Sanofi, Abbott, Bayer, Medtronic, and Roche. TD has received honoraria from NovoNordisk, Lilly, Sanofi, Medtronic, Biodel, Bekton Dickinson, Boehringer, and Roche. TB has received honoraria from NovoNordisk, Lilly, Sanofi, and Medtronic. HJB has received honoraria and lecture fees from Novo Nordisk, Lilly, Sanofi, Medtronic, and Roche. LD has received research support from Novo Nordisk and Advisory Groups for Sanofi. The remaining authors (TU, BS, and LM) have declared no potential conflicts. Editors of the ISPAD Clinical Practice Consensus Guidelines 2014 Compendium: Carlo Acerini, Maria Craig, David Maahs, and Ragnar Hanas.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Nutritional management in children and adolescents with diabetes

Smart CE, Annan F, Bruno LPC, Higgins LA, Acerini CL. Nutritional management in children and adolescents with diabetes.

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- Nutrition therapy is recommended for all children and adolescents with type 1 diabetes. Implementation of an individualized meal plan with appropriate insulin adjustments can improve glycemic control (A).
- Dietary recommendations are based on healthy eating principles suitable for all children and families with the aim of improving diabetes outcomes and reducing cardiovascular risk (E).
- Nutritional advice should be adapted to cultural, ethnic, and family traditions, as well as the cognitive and psychosocial needs of the individual child (E).
- A specialist pediatric dietician with experience in childhood diabetes should be part of the interdisciplinary team and should be available as soon as possible at diagnosis to develop a lasting trusting relationship (E).
- Energy intake and essential nutrients should aim to maintain ideal body weight, optimal growth, health and development and help to prevent acute and chronic complications. Growth monitoring is an essential part of diabetes management (C).
- The optimal macronutrient distribution varies depending on an individualized assessment of the young person. As a guide, carbohydrate should approximate 50–55% of energy, fat <35% of energy (saturated fat <10%), and protein 15–20% of energy (C).
- Matching of insulin dose to carbohydrate intake on intensive insulin regimens allows greater flexibility in carbohydrate intake and meal times, with potential for improvements in glycemic control and quality of life (B). However, regularity in meal times and eating routines are still important for optimal glycemic outcomes (C).
- There are several methods of quantifying carbohydrate (CHO) intake (gram increments, 10–12 g CHO portions and 15 g CHO exchanges). There is no strong research evidence to suggest that one particular method is superior to another (E).
- Fixed insulin regimens require consistency in carbohydrate amount and timing to improve glycemic control and reduce the risk of hypoglycemia (C).
- The use of the glycemic index (GI) provides additional benefit to glycemic control over that

observed when total carbohydrate is considered alone (B).

- Dietary fat and protein may impact postprandial glycemia (A). Randomized controlled trials of methods to manage hyperglycemia after meals high in fat and protein are required (E).
- Prevention of overweight and obesity in pediatric type 1 diabetes is a key strategy of care and should involve a family based approach (B).
- Weight loss or failure to gain appropriate weight may be a sign of illness (infections, celiac disease, and hyperthyroidism), insulin omission or disordered eating (C).
- Nutritional advice should be provided on how to cope successfully with physical activity, exercise, and competitive sports (E).
- Nutritional management of type 2 diabetes requires a family and community approach to address the fundamental problems of excessive weight gain, lack of physical activity, and the increased risk of cardiovascular disease (E).
- There is a need for more research and evaluation of dietetic management in childhood diabetes (E).

Introduction

Nutritional management is one of the cornerstones of diabetes care and education. Different countries and regions have widely varying cultures and socio-economic status that influence and dominate dietary habits. Although there is strong evidence for nutritional requirements in young people the scientific evidence base for many aspects of diabetes dietary management is still emerging and it is important to individualize nutrition interventions and meal plans.

These consensus guidelines reflect national and international pediatric position/consensus statements (1–3) and evidence derived from recommendations for adults with diabetes (4–6). Further research is required in many areas of pediatric diabetes management and education particularly in effective nutrition therapy interventions and long-term outcomes.

Dietary recommendations for children with diabetes are based on healthy eating recommendations suitable for all children and adults (2, 3) and therefore the whole family. Nutritional advice must be adapted to cultural, ethnic and family traditions, and the psychosocial needs of the individual child. Likewise the choice of insulin regimen should take into account the dietary habits and lifestyle of the child.

A specialist pediatric dietician with experience in childhood diabetes should be available as part of a pediatric interdisciplinary diabetes care team to provide education, monitoring and support to the child, parents, carers, extended family, nursery, school teachers, and babysitters. Regularity in meal times

and routines where the child and family sit down and eat together help to establish better eating practices and monitoring of food intake has been shown to be associated with better glycemic outcomes (7–9).

Nutrition therapy, when used in combination with other components of diabetes care, can further improve clinical and metabolic outcomes (10, 11). The dietician should advise on planning, content and the timing of snacks/meals in the context of each child's individual circumstances, lifestyle and the insulin action profiles. It is important that the whole family is involved in making appropriate changes based on healthy eating principles. The impact of diabetes on eating behavior must not be underestimated and may cause psychological disturbance. Therefore, experienced professionals should facilitate dietary and lifestyle changes. Education should include behavior change approaches, motivational interviewing and/or counseling and should be regularly reviewed to meet the constantly changing needs and requirements of the developing child. In order to be most effective, the dietician needs to develop a consistent, trusting, and supportive relationship with the families concerned (12, 13) and also have clear agreed goals with the interdisciplinary team (14).

Nutrition education and lifestyle counseling should be adapted to individual needs and delivered in a patient-centered manner. Education can be delivered both to the individual child and family and in small group settings.

These recommendations target healthy eating principles, optimum glycemic control, the reduction of cardiovascular risk factors, the maintenance of psychosocial well-being, and family dynamics.

Aims of nutritional management

- Encourage appropriate eating behavior and healthy life long eating habits while preserving social, cultural, and psychological well-being.
- Three meals a day incorporating a wide variety of nutritious foods from all food groups, with appropriate healthy snacks (if necessary), will supply all essential nutrients, maintain a healthy weight, prevent bingeing, and provides a framework for regular monitoring of blood glucose (BG) levels.
- Provide sufficient and appropriate energy intake and nutrients for optimal growth, development, and good health.
- Achieve and maintain an appropriate body mass index (BMI) and waist circumference. This includes the strong recommendation for children and young people to undertake regular physical activity.
- Achieve a balance between food intake, metabolic requirements, energy expenditure, and insulin action profiles to attain optimum glycemic control.

Nutritional management in children and adolescents

- Prevent and treat acute complications of diabetes such as hypoglycemia, hyperglycemic episodes, illness, and exercise-related problems.
- Reduce the risk of micro- and macro-vascular complications.
- Maintain and preserve quality of life.
- Develop a supportive relationship to facilitate behavior change and positive dietary modifications.

Guidelines on energy balance, energy intake, and food components

Energy balance

At diagnosis, appetite and energy intake are often high to restore preceding catabolic weight loss. Energy intake should be reduced when appropriate weight is restored (15). Monitoring by the team, particularly in the 6 weeks after diagnosis, is necessary to assess appropriate weight gain (16).

- Energy intake varies greatly within subjects on a daily basis due to age, growth rate, physical activity, and other important environmental factors such as the type and availability of food.
- Energy intake should be sufficient to achieve optimal growth and maintain an ideal body weight.
- Flexibility in the advice about the amount of food to meet varying energy needs is necessary.
- Dietary advice/meal planning should be revised regularly to meet changes in appetite and insulin regimens and to ensure optimal growth (17).
- Insulin (amount and type) should be adapted where possible to the child's appetite and eating pattern. Making a child eat without an appetite or withholding food in an effort to control BG should be discouraged as this may adversely impact growth and development (17).
- During puberty, energy intake and nutritional demands increase substantially along with significant increase in insulin dosage.

Weight maintenance

- Energy intake may be regulated by appetite, but when food is in abundance excess energy intake contributes to obesity.
- The prevalence of childhood obesity is increasing rapidly worldwide (18). This is caused by a combination of overnutrition and insufficient physical activity. For children with diabetes other contributing factors may include overinsulinization, snacking, and excess energy intake to avoid or treat hypoglycemia.
- Prevention of overweight/obesity is a key strategy of care. Guidance on family food choices, appropriate

portion sizes, energy density of foods, meal routines, and physical activity is essential (2).

- Children with diabetes at all ages and in both sexes have been reported to be heavier than their peers without diabetes (19). More recent studies have demonstrated similar rates of overweight and obesity as the general population (20, 21).
- Important aspects of management in the prevention of overweight are:
 - Plotting the growth curve, BMI (18), and if possible waist circumference every 3 months. Currently there are no international reference ranges for waist circumference in children <16 yr. Target reference values for young people aged ≥16 yr are <80 cm for females and <94 cm for males (22).
- Regular review by a dietician.
- Promotion of regular moderate-vigorous physical activity for 60 min/d on a daily basis (23).
- Consistent advice on the prevention and appropriate treatment of hypoglycemia (to prevent overtreatment) by all team members.
- Adjustment of insulin in preference to intake of additional food for hypoglycemia prevention in the management of physical activity.
- Review of the insulin regimen to minimize hypoglycemia and the need for large snacks.
- Psychological counseling should be given to young people with disordered eating/eating disorders.

Energy intake recommendations

A guide to the distribution of the total daily energy intake is as below. However, the optimal macronutrient distribution may vary depending on an individualized assessment of the young person. National guidelines for adults and children with diabetes in Australia and Canada recommend a carbohydrate intake of 45–60% energy (2, 6). However, with a lower carbohydrate intake the quality of fat becomes more important. Dietary studies of children with diabetes have found that as carbohydrate intake decreases children tend to consume more saturated fat (32–35).

- Carbohydrate 50–55% (3)
- Moderate sucrose intake (up to 10% total energy) (6)
- Fat 25–35%
- <10% saturated fat + trans fatty acids
- <10% polyunsaturated fat
- >10% monounsaturated fat (upto 20% total energy) (5)
- Protein 15–20% (2, 3)

Food components

Carbohydrates

There is international agreement that carbohydrate should not be restricted in children and adolescents with type 1 diabetes as it may result in deleterious effects on growth.

- Caregivers should encourage healthy sources of carbohydrate foods such as whole grain breads and cereals, legumes (peas, beans, and lentils), fruit, vegetables, and low-fat dairy products (full fat in children under 2 yr).

Sucrose

Sucrose and sucrose-containing food should be eaten in the context of a healthy diet, and the intake of other nutrients ingested with sucrose, such as fat, should be taken into account (4).

Sucrose does not increase glycemia more than isocaloric amounts of starch (24). Sucrose can be substituted in moderation for other carbohydrate sources without causing hyperglycemia. If added, sucrose should be appropriately balanced against insulin doses (17).

Sucrose should provide up to 10% of total daily energy intake (6). Not all countries have a specific recommendation on the percentage of sugar or monosaccharide or disaccharides in the diet.

- Sucrose sweetened beverage consumption has been linked to excessive weight gain (25). Large quantities of sugary beverages are difficult to adequately cover with insulin and may cause hyperglycemia. Diet or light drinks can safely be recommended for children with diabetes instead of sugary drinks on special occasions.
- Sucrose may be used instead of glucose to prevent or treat hypoglycemia. See guideline on hypoglycemia for more details.

Fiber

- Estimates of dietary fiber intakes in children in many countries are lower than recommended (27).
- The recommendation (3.3 g of fiber per megajoule) gives a higher amount of fiber per day.

Age	Fiber recommendations
Birth to 1 yr	Not determined
≥ 1 yr (26)	14 g/4184 kJ (1000 kcals) 3.3 g/MJ
Alternatively Children >2 yr old (27)	Age in years + 5 = grams of fiber per day

- Intake of a variety of fiber containing foods such as legumes, fruit, vegetables, and wholegrain cereals should be encouraged. Soluble fiber in vegetables, legumes, and fruit may be particularly useful in helping to reduce lipid levels (28, 29),
- Fruit pectin may also be useful in enhancing the protection against cardiovascular disease (30).
- Insoluble fiber found in grains and cereals promotes healthy bowel function.
- Fiber should be increased slowly in the diet to prevent abdominal discomfort.
- Any increase in fiber intake should be accompanied by an increase in fluid intake.
- Higher fiber foods may help to improve satiety and replace more energy dense foods.
- Processed foods tend to be lower in fiber therefore, unprocessed, fresh foods should be encouraged.

Fats

Population-based nutritional guidelines recommend a fat intake of no greater than 30–35% total daily energy intake (31). A range of recommendations currently exist in adult guidelines, from no specific recommendation for percentage total energy up to 35% energy from fat (2, 4, 6). High total fat intakes have been shown to increase the risk of overweight and obesity (31). High saturated and trans fat intakes have been linked to an increased risk of cardiovascular disease (2, 32). Studies have shown children and young people with diabetes have consumed fat and saturated fat above dietary recommendations (32–35).

The primary goal regarding dietary fat in clinical practice is usually to decrease the intake of total fat, saturated fat, and trans fatty acids. Monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) can be used as substitutes to improve the lipid profile (5).

- Care should be taken when giving dietary education that methods of quantifying carbohydrate do not increase total fat and/or saturated fat intake.

Saturated fat and trans fatty acids

- Recommendations for saturated and trans fatty acids should be in line with those for the general population. No more than 10% energy from saturated fat and trans fatty acids is recommended (36). Saturated fat is the principal dietary determinant of plasma low-density lipoprotein (LDL) cholesterol. Saturated fats are found in full fat dairy products, fatty meats, and high-fat snacks. Trans fatty acids, formed when vegetable oils are processed and solidified (hydrogenation), are found in margarines, deep-frying fat, cooking

fat, and manufactured products such as cookies and cakes.

- Replace saturated fat with unsaturated fats by using lean meats, fish, low-fat dairy products, and changing to MUFA and PUFA cooking oils and margarines. Whole diet approaches may be useful in changing intake, for example, the Mediterranean diet (37).

MUFAs and PUFAs

- Unsaturated fatty acids are important components of lipid membranes.
- 10–20% energy from MUFA is recommended (36). MUFA (particularly *cis*-configuration), found in olive, sesame and rapeseed oils, and also in nuts and peanut butter may be beneficial in controlling lipid levels and convey some protection against cardiovascular disease. They are recommended replacements for saturated fats.
- Less than 10% energy from PUFA is recommended (36). PUFA derived from vegetable origins such as corn, sunflower, safflower, and soybean or from oily marine fish may assist in the reduction of lipid levels when substituted for saturated fat.
- Consumption of oily fish, which is rich in n-3 fatty acids, is recommended. Advice for children is to eat oily fish once or twice weekly in amounts of 80–120 g (38, 39).
- n-3 supplements or an increase in the intake of oily fish should be considered if triglyceride levels are elevated.
- The use of plant sterol and stanol esters (in margarine and dairy products) may be considered for children ≥ 5 yr if total and/or LDL cholesterol remains elevated (40, 41).

Hyperlipidemia

Management of hyperlipidemia requires a comprehensive approach (42):

- Initial therapy should be to optimize glucose control.
- Medical nutrition therapy to reduce saturated fat intake to less than 7%, and increase dietary sources of both soluble fiber and anti-oxidants.
- Lifestyle changes (control weight and increase physical activity) and if applicable, discontinue tobacco use.
- Only if glucose control and/or lifestyle cannot be optimized, or hyperlipidemia persists despite these measures, should pharmacological treatment be considered (see guideline on Chronic Complications).

Protein

- Intake decreases during childhood from approximately 2 g/kg/d in early infancy to

1 g/kg/d for a 10 yr old and to 0.8–0.9 g/kg/d in later adolescence(43).

- Worldwide intake of protein varies greatly depending on economy and availability.
- Protein promotes growth only when sufficient total energy is available.
- High protein diets, >25% energy, are not generally advised for children with type 1 diabetes as they may impact growth and vitamin and mineral intake.
- High protein drink and food supplements are generally unnecessary for children with diabetes. Their use requires dietary review with individualized advice.
- Sources of vegetable protein such as legumes should be encouraged. Sources of animal protein also recommended include fish, lean cuts of meat, and low-fat dairy products (2).
- When persistent microalbuminuria or established nephropathy occurs, excessive protein intake (>25% energy) may be detrimental. It is prudent to advise that intake should be at the lower end of the recommended range (5). However, there is insufficient evidence to restrict protein intake. Any modifications to protein intake in adolescence should not be allowed to interfere with normal growth and requires expert management by a dietician.

Vitamins, minerals, and antioxidants

Children with diabetes have the same vitamin and mineral requirements as other healthy children (2).

There is no clear evidence of benefit from vitamin or mineral supplementation in children with diabetes who do not have underlying deficiencies.

It is recommended that individualized meal planning include optimization of food choices to meet recommended dietary allowance/dietary reference intake for all micronutrients.

Many fresh fruits and vegetables are naturally rich in antioxidants (tocopherols, carotenoids, vitamin C, and flavonoids) and are strongly recommended for young people with diabetes for cardiovascular protection.

Supplements such as vitamin D for young children are recommended in some countries following the national guidelines for healthy children. If vitamin D levels are low, supplementation in line with the general population should occur (44).

Salt

Children with diabetes should limit their salt intake to at least that of recommendations for the general population. A guide is 1500 mg/d (3.8 g of salt/day) for children aged ≥ 9 yr (26).

Guidelines for salt intake in younger children are 1–3 yr: 1000 mg/d (2.5 g salt/day); 4–8 yr: 1200 mg/d (3 g salt/day) (26).

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Salt is added to many processed foods (only 20% of intake is usually added at the table and in cooking).

- Salt intake is too high in many countries due to the high intake of processed foods.
- Processed foods should be decreased for the whole family and practical advice given to develop cooking skills with fresh foods.
- Dietary advice should include minimizing salt addition to cooking or meals and lower salt products/foods where practical.

Alcohol

Excess alcohol is dangerous because of suppression of gluconeogenesis and it may induce prolonged hypoglycemia in young people with diabetes (up to 10–12 or more hours after drinking, depending on the amount ingested) (45). Education on the following points should be emphasized when a child or young person starts to include alcohol in their lifestyle or prior to transition to adult services.

- Alcohol is prohibited in many societies and age restricted in most, but remains a potential problem from abuse.
- Alcohol in children may lead to increased risk-taking behaviors.
- Many types of alcoholic drinks are available, some of which are particularly targeted at young people. Education is needed on the alcohol content of different drinks.
- Carbohydrate should be eaten before and/or during and/or after alcohol intake. It may be also necessary to adjust the insulin dose particularly if exercise is performed during/after drinking.
- Advice should include drinking in moderation and practical ways to reduce alcohol intake such as the use of alcohol reduced beers.
- Low carbohydrate or ‘diabetic’ beers should be viewed with caution as many do not have reduced alcohol content.
- Special care should be taken to prevent nocturnal hypoglycemia by having a carbohydrate snack at bedtime and monitoring BG levels more often than usual during the night and the following day, at least until lunchtime (3).
- Young people should be encouraged to wear identification for diabetes.

Specially labeled diabetic foods

- Such foods are not recommended because they are not necessary, are expensive, often high in fat, and may contain sweeteners with laxative effects. These include the sugar alcohols such as sorbitol.

- Although international nutritional guidelines advise that a moderate amount of sucrose can be consumed (2–6), ‘diabetic foods’ are still for sale in some countries.

Artificial and intense sweeteners

- Water should be encouraged instead of sugary drinks and cordials.
- Sugary drinks are not encouraged as they lead to weight gain and may cause hyperglycemia as the insulin dose is commonly not matched to the carbohydrate quantity. Diet soft drinks or diet cordials are a better alternative.
- Products such as low-fat yoghurt with intense sweeteners can be useful, especially for those who are overweight.
- Saccharin, neotame, aspartame, acesulfame K, cyclamates (in some countries), alitame, and sucralose are used in low sugar, ‘light’ or ‘diet’ products to improve sweetness and palatability.
- Acceptable daily intakes (ADI) have been established in some countries.
- There are no published scientific reports documenting harm from an intake of artificial sweeteners in doses not exceeding ADI (46).

Guidelines for nutritional care, education, and meal planning

- 1 Initial dietary advice by a pediatric diabetes dietician should be provided as soon as possible after diagnosis to promote a secure, trusting, and supportive relationship (13). A dietary history should be taken including:
 - Preexisting family dietary habits, traditions, and beliefs.
 - The child’s usual food intake including energy, carbohydrate distribution and fat intake, quality of food choices, fast-foods and mealtimes, or patterns of food intake.
 - The child’s daily activities including the impact of nursery/school/college/work, physical activity, and exercise schedules.
- 2 Advice should be given at diagnosis based on the dietician’s assessment and the individualized plan provided by the diabetes team. A series of follow-up appointments should be completed with the specialist pediatric dietician within 3–6 months after diagnosis with the first review within a month after diagnosis (11). It is important that the initial or review assessment includes identification of any body image or weight concerns.
- 3 Contacts thereafter depend on local arrangements, a minimum should include two to four times in the first year and annual reassessment (11). These

are necessary to keep pace with the child's growth, diabetes management, psychosocial adaptation, lifestyle changes, and the identification of specific dietary problems such as dysfunctional eating habits, family issues around food, obesity, and eating disorders.

- 4 There is consensus that continuation of care, support, and review by a dietician is essential for optimal care.
- 5 Circumstances such as changing insulin regimen, dyslipidemia, poor dietary knowledge, excessive weight gain, and comorbidities such as celiac disease require extra education and dietary intervention with more frequent review.
- 6 Dietary education should be individualized and appropriate for the age and maturity of the child to help engage the child in active learning (47).

Education tools and methods

Education tools and methods are used to provide knowledge and skills to optimize glycemic control and cardiovascular outcomes.

- There is no international consensus on the most appropriate tools and method/s for education, although a method of carbohydrate assessment is essential.
- There are no high quality, long term, randomized studies to support one particular method of carbohydrate counting compared with another.
- BG monitoring (preprandial and postprandial) provides essential information to confirm the success of the chosen method.
- As families become more confident with managing diabetes, education should be responsive to their observations, and education on GI or insulin coverage of high fat, high protein meals may be discussed.
- As children grow and take more responsibility, regular reeducation is essential.

The following are examples of a range of tools ranging from simple to complex that can be used at various stages of education. Basic dietary education should cover healthy eating and carbohydrate assessment, with some method of carbohydrate quantification.

Healthy eating education tools

The Plate Model method (Fig. 1) is useful in providing basic nutritional information and healthy eating concepts. It also illustrates visually carbohydrate-containing foods in relation to other food components and are attractive visual aids for children. Regular meals and snacks (at least three balanced meals per day) ensures that the range of nutrients are consumed to meet daily recommended requirements (48).

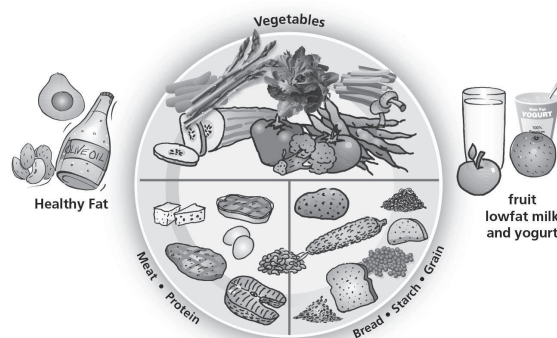


Fig. 1. Joslin Diabetes Center Healthy Plate Copyright © 2013 by Joslin Diabetes Center (www.joslin.org). All rights reserved. Reprinted with permission.

Carbohydrate assessment and methods

- The amount of carbohydrate and available insulin is one of the most important factors influencing postprandial glycemic control (4, 49).

Other dietary variables such as GI, fat, protein, and fiber impact postprandial glycemia and should be considered in interpreting and optimizing postprandial glucose levels (50–53). However, most education tools are based upon the premise that carbohydrate amount and type is recognized as the primary determinant of the postprandial response (54) and along with distribution of carbohydrate (55) form the basis of most education programs.

Extensive patient education materials are available in many countries to help adolescents and families estimate the carbohydrate content of foods in grams or exchanges or portions. Considerable time is often spent educating patients on how to read and interpret food labels, assess the carbohydrate content of the snack/meal and understand the nutrient content of foods in order to make healthy choices. Most national diabetes associations also produce useful literature on how to read food labels. It remains important to ensure that the principles of a healthy balanced diet underlie all education to not only improve glycemic control but also decrease cardiovascular risk.

Education regarding carbohydrate intake must be individualized to the child and family according to their understanding and the insulin regimen. Practical guidance on the distribution of carbohydrate intake necessary for both fixed and more flexible insulin regimes (4, 17).

Carbohydrate counting

Carbohydrate counting is a meal planning approach that focuses on carbohydrate as the primary nutrient affecting postprandial glycemic response. It aims to improve glycemic control and allow flexibility of food choices (56).

Studies in adults have reported glycemia and life-style benefits when carbohydrate counting is used as an intervention for people with diabetes (57–59). These benefits include improved glycemic control as measured by lower hemoglobin A1c (HbA1c) levels (59–62), improved diabetes-specific quality of life (59, 60), and improved coping ability in daily life (59, 61, 62).

However, it is essential that carbohydrate counting is incorporated as part of team-based approach to management and that healthy eating principles and routines underlie all education. Furthermore carbohydrate counting should not be seen as an emphasis on one nutrient only and dietary quality remains important (63).

Three levels of carbohydrate counting have been identified by the American Academy of Nutrition and Dietetics (64).

- *Level 1:* Consistent carbohydrate intake. This level introduces the basic concept of carbohydrate as the food component that raises BG. A consistent intake of carbohydrate is encouraged using exchange or portion lists of measured quantities of food. This is appropriate for those on twice daily insulin doses where a consistent carbohydrate intake from day-to-day is required (55).
- *Level 2:* Pattern management principles. This level is an intermediate step in which patients continue to eat regular carbohydrate, use a consistent baseline insulin dose and frequently monitor BG levels. They learn to recognize patterns of BG response to carbohydrate intake modified by insulin and exercise. With this understanding and team support they make adjustments to their insulin dose for food and exercise to achieve BG goals. Pediatric teams use this method less frequently, as most now employ either consistency in carbohydrate intake or insulin to carbohydrate ratios (ICRs).
- *Level 3:* ICRs. This level of carbohydrate counting is appropriate for people using multiple daily injections (MDI) or insulin pump therapy. It involves the calculation of ICR that is individualized for each child according to age, sex, pubertal status, duration of diagnosis, and activity. This enables young people with diabetes to adjust their prandial insulin dose according to carbohydrate consumption.

Many pediatric diabetes centers use only level 3 carbohydrate counting for patients on intensive insulin therapy (65).

Methods of quantifying carbohydrate in common use include:

- Gram increments of carbohydrate
- 10–12 g carbohydrate portions
- 15 g carbohydrate exchanges.

Research has not demonstrated that one method of teaching carbohydrate counting (grams, portions, or exchanges) is better than other methods (66, 67).

Studies have evaluated carbohydrate counting accuracy in the pediatric population because accurate carbohydrate counting has been demonstrated to be important to optimize postprandial glycemia (68–70). Research has shown that children, adolescents, and their parents can measure carbohydrate with a degree of accuracy, however underestimation and overestimation of foods remains a challenge (67, 69, 71). Regular review is necessary as children grow and new foods are introduced (67).

GI and glycemic load

The use of the GI has been shown to provide additional benefit to glycemic control over that observed when total carbohydrate is considered alone (72, 73). In type 1 diabetes GI should not be used in isolation, but with a method of carbohydrate quantification or regulation (74).

A controlled study in children substituting low GI for high GI foods found the lower GI diet improved glycemic control after 12 months compared with more traditional dietary advice (75).

- Low GI foods may lower postprandial hyperglycemia when they are chosen to replace higher GI foods (6). This has been demonstrated in a meal study with children using MDIs (76).
- Low GI food sources include whole-grain breads, pasta, temperate fruits, and dairy products (77).

Glycemic load (GL) is another method of predicting the postprandial BG response, which takes into account both the GI of the food and the portion size (78). There has been no assessment of its efficacy in children or adults with type 1 diabetes.

Dietary recommendations for specific insulin regimes

Conventional therapy

- Twice daily insulin regimens of short and longer acting insulin require day-to-day consistency in carbohydrate intake (often as three regular meals with snacks between) to balance the insulin action profile and prevent hypoglycemia during periods of peak insulin action (55).
- On twice daily insulin, the carbohydrate content consumed in the meals eaten at the time of the insulin doses can be flexible if the patient/family is taught to adjust the short/rapid acting insulin to the carbohydrate eaten (79). Clinical experience indicates that preprandial and

postprandial BG testing can assist with determining the appropriateness of insulin dosage changes. Prescription of carbohydrate in a fixed meal plan requires regular review in a growing child and can be unsuitable because of the daily variability of total energy and carbohydrate intake.

- Particular attention should be paid to the total energy/carbohydrate intake and timing of meals or snacks to optimize glycemic control and to prevent excessive weight gain
- Most conventional insulin regimens require carbohydrate intake before bed to help in the prevention of nocturnal hypoglycemia.

MDI therapy and pumps

A more flexible approach using individualized ICRs, which enable insulin dose to be matched to carbohydrate intake, may be used for children and adolescents on intensive insulin therapy. This approach has been endorsed by a number of international consensus guidelines (1–4, 6). In order to assess the accuracy of the ICR preprandial and 2–3 h postprandial BG testing is required. The ‘500 rule’ is often used to obtain an initial ratio, although other methods are also used (see ‘Insulin’ chapter).

This approach increases flexibility, by allowing more variable food intake at different meal times, decreasing the need for between meal snacks and allowing greater flexibility in meal times. Research suggests that a single meal time bolus of insulin may cover a range of carbohydrate intake without deterioration in postprandial control (80).

Insulin pump therapy provides the greatest degree of flexibility in meal times and a greater variation in carbohydrate intake.

- Care should be taken when an ICR is used in MDI and pump therapy, that the overall quality of the diet is not reduced (63).
- Increased flexibility should not mean total freedom without consideration of healthy eating principles and meal-time routines (9).

Studies in adults using MDI with ICRs have shown improvements in dietary freedom, glycemic control, and quality of life (57, 58, 60), particularly if delivered as part of a comprehensive education package. ICRs have also been evaluated in children and adolescents using MDI, often as part of structured education programs (47, 81–85). The results have been variable some indicating improvement in glycemic control and others not, but most have reported improved quality of life outcomes.

The use of meal time insulin bolus calculators in both MDI and pump therapy has been shown to

assist insulin dose calculations and potentially improve postprandial glycemia (86, 87).

Rapid acting insulin analogs are usually given in these regimens immediately before meals to diminish the postprandial BG-excursion (88) and to decrease the likelihood of being forgotten (89). In addition, snacks without meal boluses are common in adolescents and result in deterioration in glycemic control (90). Giving insulin boluses after a meal (91) and frequent snacking (9) have also been shown to worsen glycemic control.

- For those on MDI clinical experience at some centers suggests short-acting (regular/soluble) insulin may be given when a prolonged insulin effect is desired to match certain meals (e.g., high fat, carbohydrate dense foods). Preprandial and postprandial BG testing should be used to evaluate this regimen.
- One of the advantages of pump therapy is its ability to tailor prandial insulin delivery to the meal composition. This enables the meal bolus to match the glycemic effect of the meal (low GI and/or high-fat or high-protein content). For high-fat carbohydrate dense meals such as pizza and battered fish and chips, the dual wave bolus has been shown to most effectively match the postprandial glycemic profile (92, 93). Additionally, a dual-wave bolus prior to a low GI meal was found to significantly reduce the postprandial glucose excursion (94).
- Continuous glucose monitoring systems can be useful in guiding insulin adjustments to match the glycemic responses of different meals (95).
- To date, the meal-time insulin dose is typically calculated using an individualized ICR. However, there is increasing evidence that the impact of other macronutrients (fat and protein) should be considered when determining the bolus insulin dose and delivery (50, 52, 53, 96).

Recent studies in both children and adults using intensive insulin therapy have shown that meals high in protein or fat increase delayed hyperglycemia (53, 96). These studies highlight the limitations of current carbohydrate-based algorithms for insulin dosage calculations. The calculation of fat and protein units has been suggested to cover the postprandial excursions caused by high fat and protein meals (97, 98). Another novel insulin dosing algorithm based on the Food Insulin Index, has also been developed and trialed in adults (99).

Randomized controlled trials of methods to manage delayed postprandial glycemia after meals high in fat and protein are required, in addition to evaluating their acceptability to individuals with diabetes.

Age-group-specific advice

The challenges of nutrition education for children and adolescents with diabetes are often age-related and require consideration of the specific nutrition and developmental needs for different age groups. The defining characteristics of different age groups must be considered when providing nutrition care to children and adolescents. Below is a summary of some of the specific characteristics to consider when working with different age groups.

Toddlers

- Toddlers have variable appetites. Routine, small meals over the day may promote better glycemic control and nutritional adequacy. Discourage continual eating as this may contribute to food refusal issues at meal-times and can lead to difficulty in interpreting BG levels.
- Insulin pump therapy may be effective in helping manage toddler-eating behaviors (8, 100). It is preferable that preprandial insulin doses are given, although the dose can be split to preprandial and during the meal when eating is erratic or new foods are offered.
- Positive parental role models and early participation in family meals may promote improved cooperation regarding food and healthy food choices. Discourage the reintroduction of a bottle of milk or juice for 'easy' carbohydrate intake.
- A variety of tastes, colors, and textures of foods should be encouraged.
- Parental anxiety regarding food intake is common in this age group and consideration of this needs to be given when deciding on an insulin regimen. Daycare providers need instruction on diabetes management.

School aged children

Meal and snack routine ideally should be incorporated into the usual school timetable.

The child should start to acquire an understanding of carbohydrate amounts in foods with supervision and support (67).

- Individual advice should be provided regarding carbohydrate intake to prevent hypoglycemia particularly for school events such as sports days, excursions, and camps. This should not be needed for the child's usual active play.
- Advice on healthy food choices, food portion size, and physical activity to reduce the risks of inappropriate weight gain and cardiovascular disease is important.
- Sleepover and party advice should be discussed.

- School personnel need understanding and training in diabetes management.

Adolescents

Challenging behaviors may include staying out late, sleeping in, skipping insulin, missing meals and in some cultures, drinking alcohol.

Emphasis should be placed on the importance of healthy, family-based meals particularly during periods of rapid growth to prevent excessive afternoon or evening snacking.

Negotiations and consideration of the insulin management regime to suit variable schedules, including school, exercise, and work commitments is an important consideration.

Weight monitoring is recommended for early recognition of either weight loss or inappropriate weight gain.

- Excessive weight gain requires careful review of insulin dosage, food intake, glycemic control, and physical activity.
- Weight loss or failure to gain weight may be associated with insulin omission for weight control and may be indicative of a disordered eating behavior or an eating disorder (see below). In those with high HbA1c, irrespective of weight profile, further assessment of disordered eating thoughts and behaviors should be considered.

Parties, vacations, peer pressure to eat inappropriately, and healthy lifestyle advice all require discussion, problem solving, and target setting.

- Advice on the safe consumption of alcohol and the risks of prolonged hypoglycemia is important in some societies.
- Information on the nutritional content of snack and takeaways is important.

Parties, festivities, and special events. Special dispensation is usually given to children with diabetes during fasts such as Ramadan. If the family wishes to participate in fasts, education on carbohydrate and insulin adjustment needs to be provided.

Nutritional management of exercise and physical activity

Children and adolescents with diabetes should be encouraged to participate in regular physical activity because it promotes cardiovascular health and aids weight management.

Planned or unplanned physical activity is one of the commonest causes of hypoglycemia in young people

with type 1 diabetes. However, intense exercise can cause hyperglycemia during the activity, with potential for delayed hypoglycemia. See Guideline on Exercise for more details.

Children and young people undertaking regular physical activity and training have the same nutritional requirements as their peers without diabetes. Dietary intake needs to be appropriate to support growth and the demands of the specific sport (101). In addition, nutritional strategies are needed to prevent the potential hypoglycemic and hyperglycemic effects of exercise. The energy and carbohydrate demands of exercise vary with the type, intensity, and duration of exercise so an individual approach to advice is required.

Advice on physical activity, exercise, and sport should emphasize the importance of careful planning, individual attention to detail (BG monitoring, food intake, and insulin adjustment) and incorporate the personal experiences of the young person. Advice on additional carbohydrate intake should relate to the energy and carbohydrate demand of the activity and the type and intensity of the exercise being undertaken.

Exercise should be delayed if control is poor [BG > 14 mmol/L (250 mg/dL) or if ketones are present] until the diabetes is under better control with insulin administration.

Unplanned and spontaneous activity

Hypoglycemia is commonly associated with unplanned physical activity. Depending on the duration and intensity of exercise, this may occur during or after exercise, in the period of increased insulin sensitivity and muscle recovery. See Guideline on Exercise for more details.

Young people with diabetes need to have rapidly absorbed carbohydrate readily available when undertaking exercise.

- If extra carbohydrate is necessary for a short-duration activity then quick acting carbohydrate as a beverage is usually most useful.
- The amount of carbohydrate required for exercise is dependent on the BG level at the start of exercise, the intensity of the exercise, the frequency of routine exercise, the prevailing insulin level, the insulin regimen, and the age and weight of the young person.
- During moderate exercise, additional carbohydrate may be consumed to prevent hypoglycemia. This will vary depending on the type of activity. The requirements will be lower if the pre-meal insulin bolus for the meal before the exercise is lowered or the exercise is performed several hours after the bolus dose has been given.

Additional carbohydrate (above general population recommendations), is only recommended when the exercise level increases above the recommended 60 min/d. Redistribution of carbohydrate intake and insulin adjustment is more appropriate for normal levels of activity.

- Carbohydrate sources or snacks for unplanned exercise should not provide an intake in excess of energy expenditure. They should be low in fat such as fruit juice, sports drinks, dried fruit, fruit bars, and cereal bars.

Following unplanned physical activity, BG testing will enable more appropriate management of variations in BG levels. Reduction of evening insulin doses may be required to prevent delayed hypoglycemia, in addition to an increase in carbohydrate intake at the meals/snacks following significant periods of activity (102). Pre-bed and overnight BG testing can guide the appropriate administration of additional carbohydrate at dinner and before bed to help prevent nocturnal hypoglycemia (103).

Although it is difficult in unplanned exercise, whenever possible, particularly for children on MDI or pumps, rapid acting insulin should be reduced prior to exercise rather than extra carbohydrate consumed, to prevent excessive weight gain.

Planned or competitive sports

Regular participation in physical activity, training, and competitive sports require careful planning and individual strategies for nutrition and insulin management. Appropriate insulin adjustment, adequate nutrition, and fluid intake are essential for optimal performance (104). Adequate amounts of carbohydrate are vital for optimal sports performance; 50–65% of total energy as carbohydrate is recommended (105).

A carbohydrate based, low-fat meal should be eaten 1–3 h prior to sport to ensure adequacy of glycogen stores and availability of carbohydrate for exercise (106). In the case of elite athletes, it may be preferable to have a meal 4 hours prior to activity to maximize glycogen stores and to help ensure only basal insulin is acting.

- Additional 'quick acting carbohydrate' may be needed prior to and during strenuous exercise lasting ≥ 60 min to maintain performance. An isotonic sports drink containing 6–8% carbohydrate may be useful during prolonged activity to address both increased fluid and carbohydrate needs (107).

An intake of up to 1.0–1.5 g carbohydrate per kg body weight per hour of exercise may be required during aerobic exercise performed during peak insulin

action, if a reduction in insulin is not performed (108). Examples of suitable carbohydrate sources for exercise include carbohydrate gels, isotonic sports drinks, fruit, and fruit juices. Additional fluid should be consumed when solid forms of carbohydrate are used during exercise.

Additional carbohydrate during exercise can cause gastrointestinal upset, so advice should be adapted to suit the individual.

- Preexercise carbohydrate consumption should be related to pre-exercise BG. The idea is to distribute the carbohydrate intake throughout the activity. However, if BG is low, carbohydrate (10–15 g) should be consumed prior to the exercise and/or appropriate adjustments made to insulin to prevent hypoglycemia. For some high intensity strenuous/anaerobic activities, pre-exercise carbohydrate may also require additional bolus insulin (103, 108).
- Exercise when the patient is underinsulinized may result in hyperglycemia and poor performance (109).
- Fluid intake should be maintained at a level appropriate to the activity to maintain optimal hydration (110). Fluid requirements in children during strenuous exercise are of the magnitude 13 ml/kg/h. The fluid should be consumed throughout the activity (111).

Post-exercise carbohydrate intake needs to be sufficient to ensure replacement of both muscle and hepatic glycogen stores, and prevent post-exercise hypoglycemia caused by increased insulin sensitivity during muscle recovery. To ensure muscle recovery it is sensible to consume a low fat, protein, and carbohydrate containing meal or snack after training. Consuming carbohydrate mixed with protein may be beneficial in the prevention of post-exercise hypoglycemia (112).

Nutritional management of type 2 diabetes in children and young people

In young people with type 2 diabetes and insulin resistance, the presence of multiple cardiovascular risk factors is likely to be associated with earlier severe complications (113).

Aims of nutritional management:

- Achieve normal glycemia and HbA1c (11, 17).
- Prevent further weight gain in those with BMI at 85th–95th percentile or achieve weight loss for those with BMI >95th percentile while maintaining normal linear growth (114).
- Address comorbidities, such as hypertension and dyslipidemia (115).

Treatment recommendations

There is little evidence regarding the nutritional treatment of type 2 diabetes in children. Therefore, recommendations are derived from the treatment of overweight and obese children, type 2 diabetes in adults, and type 1 diabetes in children.

- Most children with type 2 diabetes are overweight or obese, therefore treatment should be centered on education and lifestyle interventions to prevent further weight gain or achieve weight loss with normal linear growth.
- The entire family should be included in the lifestyle intervention, as parents and family members influence the child's food intake and physical activity, and they are often overweight or obese and have diabetes as well. Studies indicate that a family approach to treatment of overweight is likely to be most effective (116, 117). Interventions have shown improved outcomes from including parents as positive role models in encouraging healthy food choices and changing behaviors to increase physical activity.
- Families should be counseled to decrease energy intake by focusing on healthy eating, strategies to decrease portion sizes of foods, and lowering the intake of high energy, fat and sugar containing foods. Simply eliminating high sugar and high energy beverages such as soft drinks and juices can accomplish improvement in blood sugars and weight (118).
- Increasing energy expenditure by increasing daily physical activity to 60 min is an important component of treatment (115). Limiting sedentary behaviors, such as television viewing and computer use has been shown to be an effective way to increase daily physical activity and help maintain or achieve a healthy weight in children (119). Physical activity may also help lower lipids in adolescents with diabetes (120).
- An interdisciplinary approach including a physician, diabetes nurse educator, dietician, mental health provider, and exercise physiologist (if possible) is recommended.
- An individualized meal plan incorporating low fat and energy choices and carbohydrate management may assist weight loss and BG targets.
- Children on MDI or pump therapy should be taught to adjust insulin to carbohydrate intake using an ICR (121). This may be helpful in reducing the need for snacks and large meals.
- Substitution of low GI foods for high GI foods may assist with control of appetite, weight, and lipid levels in adolescents with type 2 diabetes (72).
- Regular follow-up is essential to monitor weight, glycemic control, and adherence to the meal plan.

Celiac disease

Celiac disease is more common in children with type 1 diabetes than in the general population. Prevalence ranges from 0.6 to 16.4% of children with diabetes (122, 123). It is often asymptomatic (124), although may be associated with poor growth, delayed puberty, nutritional deficiencies, hypoglycemia, and hyperglycemia (125). A gluten-free diet (GFD) is the only accepted treatment for celiac disease. It is common for people with diabetes who develop celiac disease to have challenges with adherence to the GFD and improved understanding of the diet may assist adherence (126).

The GFD requires elimination of wheat, rye, barley, triticale, possibly oats, and products derived from these grains. Alternatives such as potato, rice, soy, tapioca, maize, buckwheat, and products derived from these and other gluten-free grains must be used as substitutes.

The inclusion of oats in the GFD remains controversial. Short- and long-term studies involving children and adults suggest that oats can be safely included for the majority of people (127–129). However a small minority of people with celiac disease have been found to react to oats (130). Concern also remains about cross-contamination of oats with gluten containing products. Thus the use of oats is not widely recommended in some countries. Research supports the view that contamination free oats may be acceptable for the majority but not all children with celiac disease (131).

There is debate as to the accepted definition of a GFD. It is now generally accepted in Europe and some other countries such as Canada and USA that foods containing less than 20 parts per million (ppm) gluten are suitable for a GFD (even if gluten is detectable) in accordance with Codex Alimentarius (International Food Standards).

Wheat starch is used in some European countries as part of a GFD (132). This too is controversial; as wheat starch is not recommended for inclusion in some countries such as Australia even at levels less than 20 ppm. In addition to advice on foods allowed or to avoid, emphasis should be placed on the nutritional quality of the GFD, particularly iron, calcium, fiber, and vitamin B intakes (133).

Children with diabetes and celiac disease require more frequent review by a pediatric dietician with experience in GFDs.

Eating disorders and diabetes

A range of screening questionnaires and structured clinical interviews are available to help identify and diagnose eating disorders in children and young people with diabetes (134–136).

Disordered eating and disturbed eating behavior is more common in young people with type 1 diabetes than their peers without diabetes (137). Diabetes is unique in making it possible for weight and shape control without overt avoidance of food. Insulin omission for weight control has been reported in pre-teens, adolescents, and young adults (138–140). It is increasingly recognized that adolescents may manipulate their insulin dose and/or diet because of weight and shape concerns, in ways that may not be immediately or easily identified as symptoms of an eating disorder.

It is well recognized that poor glycemic control may reflect insulin omission in association with disordered eating. This may be driven by weight concerns as well as additional emotional disorders (141). Eating disorders in adolescents and young adults with diabetes are associated with poor metabolic control and diabetic complications (142). This association is even more of a concern in young people with an increased risk of early onset of diabetic complications and evidence of ineffectiveness of treatment for the eating disorder (143).

Clinicians working with young people with diabetes and eating disorders need to consider the insulin regimen and potential for omission, metabolic control, dietary requirements, food manipulation, body dissatisfaction, and family functioning as well as high frequency of hospital admissions and/or failure to attend clinic appointments.

Interventions

An interdisciplinary approach to treatment is considered the standard of care for both eating disorders and diabetes. Close liaison with the Specialist Eating Disorder team may be required (144). More research is needed to assess the value of interventions to treat or prevent eating disorders in diabetes. A randomized controlled trial designed to specifically address eating disorder symptoms in young females with diabetes, found that an intervention was helpful for the eating disorder symptoms but did not improve either metabolic control or insulin omission (145).

Techniques may be important which enable young people to focus on positive skills in order to take control of the eating disorder and diabetes and empower families to continue to participate in the day today management of diabetes. All members of the team should have a degree of familiarity with these therapeutic approaches (144).

Behavioral approaches in diabetes dietary education

The management of diabetes in children is recognized as requiring a team approach, and parents are in need

of understanding and support from all health care professionals (146).

Family functioning and interactions at mealtimes have been demonstrated to impact on eating behavior and glycemic control in younger children (147, 148). Adolescence represents a critical stage in the development of self-management of food intake and diabetes, accompanied by independent decisions about health and lifestyle choices. It is known that psychological issues such as behavior disorders and depression are greater in children with diabetes, and this in turn is associated with poor metabolic control (149). Risk-taking behaviors, eating disorders, and non-adherence to diabetes regimens are common (150).

Systematic reviews have shown that psycho-educational interventions provide a model of patient care that has small to medium beneficial effects on glycemic and behavioral outcomes (151, 152). Further studies have shown the benefit of using behavioral techniques such as empowerment, cognitive behavioral therapy, and motivational interviewing (153, 154).

Family communication is also important and structured education programs which support open communication about diabetes and regular renegotiation of roles and shared family responsibilities throughout adolescence may be more effective than skills training alone (154). It is important that these approaches are employed as part of routine care from diagnosis, to enable children, young people, and families to develop effective self-management skills (155). A recent study has demonstrated that these approaches introduced to children and families with established diabetes may improve quality of life, however, only those with the poorest control benefited in terms of improvement in HbA1c (156).

- Pediatric dietitians should be trained in family communication skills, counseling, psychology, behavior modification approaches, and motivational interviewing.
- Training in behavioral and psychological skills would enable earlier identification of those children and families who may be struggling with food- or weight-related issues and allow earlier referrals to specialist care such as, psychologists, eating disorder teams, and child and family therapists.

Research

- There is a lack of high quality, randomized controlled trials in many aspects of nutritional management.
- Metabolic, quality of life outcomes, and the effectiveness of educational methods in relation to dietetic interventions need to be rigorously examined.

Summary

The nutritional care of children with diabetes is complex. Diabetes management is set within the context of the family, a surrounding social system, issues of non-adherence, peer pressure, emerging independence, and the ultimate aim of maintaining quality of life. It requires a deep understanding of the relationship between treatment regimens and changing physiological requirements, including growth, fluctuations in appetite associated with changes in growth velocity, varying nutritional requirement and physical activity.

Evidence suggests that it is possible to improve diabetes outcomes through attention to nutritional management and an individualized approach to education. This requires a clear focus on dietary goals in relation to glycemic control and the reduction in cardiovascular risk.

The fundamental premise of successful dietary outcomes is the development of a trusting relationship between the health professional, child, and care providers, which facilitates behavior change during the challenges of childhood and adolescent development.

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Conflicts of interest

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Diabetic ketoacidosis and hyperglycemic hyperosmolar state

Wolfsdorf JI, Allgrove J, Craig ME, Edge J, Glaser N, Jain V, Lee WWR, Mungai LNW, Rosenbloom AL, Sperling MA, Hanas R. A Consensus Statement from the International Society for Pediatric and Adolescent Diabetes: Diabetic ketoacidosis and hyperglycemic hyperosmolar state.
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Executive summary and Recommendations

The **biochemical criteria** for the diagnosis of diabetic ketoacidosis (DKA) are:

- Hyperglycemia [blood glucose (BG) >11 mmol/L (≈200 mg/dL)]
- Venous pH < 7.3 or bicarbonate < 15 mmol/L
- Ketonemia and ketonuria.

The **clinical signs of DKA** include:

- Dehydration (which may be difficult to detect)
- Tachycardia
- Tachypnea (which may be mistaken for pneumonia or asthma)

- Deep, sighing (Kussmaul) respiration; breath has the smell of acetone (variously described as the odor of nail polish remover or rotten fruit)
- Nausea, vomiting (which may be mistaken for gastroenteritis)
- Abdominal pain that may mimic an acute abdominal condition
- Confusion, drowsiness, progressive reduction in level of consciousness and, eventually, loss of consciousness.

Risk factors for DKA in newly diagnosed cases include younger age (<2 yr), delayed diagnosis, lower socioeconomic status, and countries with low prevalence of type 1 diabetes mellitus.

Risk factors for DKA in patients with known diabetes include insulin omission, poor metabolic control, previous episodes of DKA, gastroenteritis with persistent vomiting and inability to maintain hydration, psychiatric (including eating) disorders, challenging social and family circumstances, peripubertal and adolescent girls, limited access to medical services, failures in insulin pump therapy.

The following recommendations are based on currently available evidence and are intended only as a general guide to DKA management. Because there is considerable individual variability in presentation of DKA (ranging from mild with only minimal dehydration to severe with profound dehydration), some patients may require specific treatment that, in the judgment of the treating physician, may be within or, occasionally, outside the range of options presented here. Clinical judgment should always be used to determine optimal treatment of the individual patient, and timely adjustments to treatment (insulin dose, electrolyte composition and rate of infusion of rehydration fluids) should be based on ongoing, careful clinical and biochemical monitoring of the patient's response.

Emergency assessment should follow the general guidelines for Pediatric Advanced Life Support (PALS) and includes: immediate measurement of BG, blood or urine ketones, serum electrolytes, blood gases and full blood count; assessment of severity of dehydration and level of consciousness (E). A second peripheral IV catheter should be inserted (E).

Management should be in centers experienced in the treatment of DKA in children and adolescents and where vital signs, neurological status and laboratory results can be monitored frequently (E). Where geographic constraints require that management be initiated in a center with less experience and with fewer resources, there should be arrangements in place for telephone or videoconference support from a physician with expertise in DKA (E).

Meticulous monitoring of the clinical and biochemical response to treatment is necessary so that timely adjustments in treatment can be made when indicated by the patient's clinical or laboratory data (E).

Goals of therapy are to correct dehydration, correct acidosis and reverse ketosis, slowly correct hyperosmolality and restore BG to near normal, monitor for complications of DKA and its treatment, and identify and treat any precipitating event.

Fluid replacement should begin before starting insulin therapy. Expand volume, as required, to restore peripheral circulation (E). Calculate the subsequent rate of fluid administration, including the provision of maintenance fluid requirements, aiming to replace the estimated fluid deficit evenly over 48 h. The rate of fluid administration should

seldom exceed 1.5–2 times the usual daily maintenance requirement (C).

Insulin therapy: begin with 0.05–0.1 U/kg/h 1–2 h AFTER starting fluid replacement therapy (C, B).

Potassium: If the patient is hyperkalemic, *defer* potassium replacement therapy until urine output is documented. Otherwise, begin with 40 mmol potassium/L in the infusate or 20 mmol potassium/L in the patient receiving fluid at a rate >10 mL/kg/h (E).

Bicarbonate administration is not recommended except for treatment of life-threatening hyperkalemia (B).

Warning signs and symptoms of cerebral edema include: headache (variable severity) and slowing of heart rate, change in neurological status (restlessness, irritability, increased drowsiness, incontinence), specific neurological signs (e.g., cranial nerve palsies), rising blood pressure and decreased oxygen saturation.

In patients with multiple risk factors for cerebral edema, have mannitol or hypertonic saline at the bedside and the dose to be given calculated beforehand (E). If neurologic status deteriorates acutely, hyperosmolar therapy should be given immediately (C).

Prevention: Management of an episode of DKA is not complete until an attempt has been made to identify and treat the cause. Recurrent DKA without a preceding febrile or vomiting illness is almost always the result of psychosocial problems and failure to take insulin (E).

The criteria for **hyperglycemic hyperosmolar state (HHS) include:**

- Plasma glucose concentration >33.3 mmol/L (600 mg/dL)
- Venous pH > 7.25; arterial pH > 7.30
- Serum bicarbonate >15 mmol/L
- Small ketonuria, absent to mild ketonemia
- Effective serum osmolality >320 mOsm/kg
- Altered consciousness (e.g., obtundation, combativeness) or seizures.

In HHS, the goals of initial fluid therapy are to expand the intra- and extravascular volume, restore normal renal perfusion and promote a gradual decline in serum sodium concentration and osmolality.

In HHS, insulin administration should begin at a dose of 0.025 to 0.05 U/kg/h once plasma glucose is no longer declining at a rate of at least 3 mmol/L (50 mg/dL) per hour with fluid alone (C).

Diabetic ketoacidosis (DKA) results from deficiency of circulating insulin and increased levels of the counterregulatory hormones: catecholamines, glucagon,

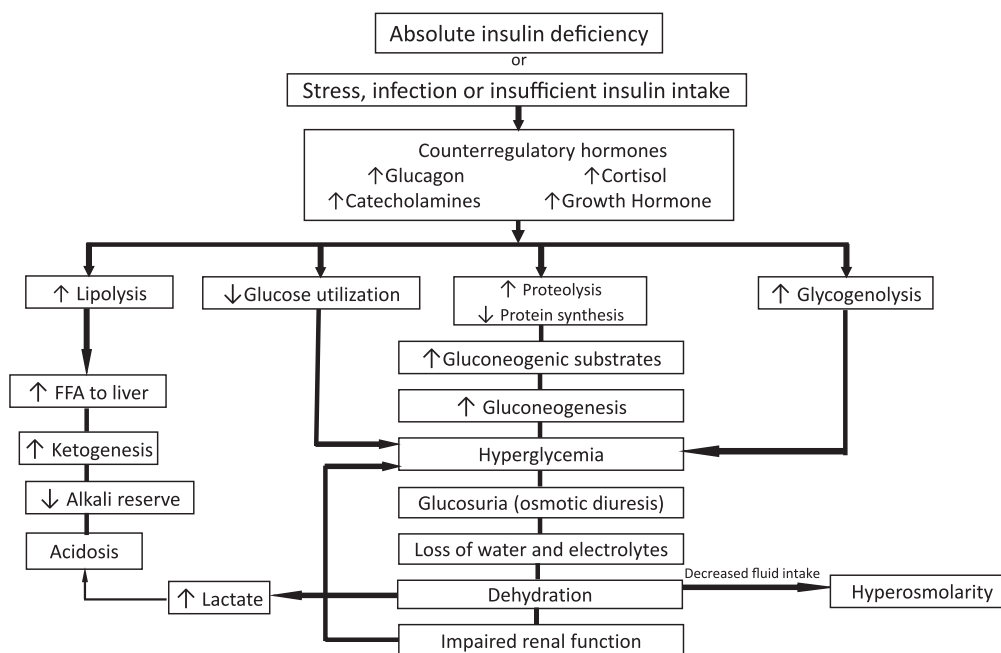


Fig. 1. Pathophysiology of diabetic ketoacidosis. Reprinted with permission from Wolfsdorf et al. (232).

cortisol and growth hormone (1, 2). Severe insulin deficiency occurs in previously undiagnosed type 1 diabetes mellitus and when patients on treatment deliberately or inadvertently do not take insulin, especially the long-acting component of a basal-bolus regimen. Patients who use an insulin pump can rapidly develop DKA when insulin delivery fails for any reason (3). Relative insulin deficiency occurs when the concentrations of counterregulatory hormones markedly increase in response to stress in conditions such as sepsis, trauma, or gastrointestinal illness with diarrhea and vomiting, which overwhelm homeostatic mechanisms and lead to metabolic decompensation despite the patient taking the usual recommended dose of insulin.

The combination of absolute or relative insulin deficiency and high counterregulatory hormone concentrations results in an accelerated catabolic state with increased glucose production by the liver and kidney (via glycogenolysis and gluconeogenesis), and simultaneously impaired peripheral glucose utilization, which combine to result in hyperglycemia and hyperosmolality; insulin deficiency and high counterregulatory hormones also increase lipolysis and ketogenesis and cause ketonemia and metabolic acidosis. Hyperglycemia that exceeds the usual renal threshold of approximately 10 mmol/L (180 mg/dL) (the range in normal and diabetic individuals varies) together with hyperketonemia cause osmotic diuresis, dehydration, and obligatory loss of electrolytes, often aggravated by vomiting associated with severe ketosis. These changes stimulate further stress hormone production, which induces more severe insulin resistance

and worsening hyperglycemia and hyperketonemia. If this cycle is not interrupted by exogenous insulin as well as fluid and electrolyte therapy, fatal dehydration and metabolic acidosis will ensue. Lactic acidosis from hypoperfusion or sepsis contributes to the acidosis (4) (Fig. 1).

DKA is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid (ECF) compartments; the range of losses is shown in Table 1. Despite their dehydration, patients generally continue to maintain normal or even have high blood pressure (5), possibly due to elevated plasma catecholamine concentrations, increased release of antidiuretic (ADH) in response to hyperosmolality, which increases blood pressure via V2 receptors, or other factors (5). Considerable urine output persists because of glucosuria until extreme volume depletion leads to a critical decrease in renal blood flow and glomerular filtration. At presentation, the specific deficits in an individual patient vary depending upon the duration and severity of illness, the extent to which the patient was able to maintain intake of fluid and electrolytes, and the content of food and fluids consumed before coming to medical attention. Consumption of fluids with a high-carbohydrate content (juices or sugar containing soft drinks) may exacerbate the hyperglycemia (6). Rapid emptying of stomach contents containing an abundant quantity of sugar, which occurs as gastroparesis is relieved with therapy, accounts for the rise in plasma glucose concentration observed in some patients after onset of therapy despite ongoing large loss of glucose in the urine (7).

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Table 1. Losses of fluids and electrolytes in diabetic ketoacidosis and maintenance requirements in normal children

	Average (range) losses per kg		24-h maintenance requirements
Water	70 mL (30–100)	≤10 kg* 11–20 kg >20 kg	100 mL/kg/24 h 1000 mL + 50 mL/kg/24 h for each kg from 11–20 1500 mL + 20 mL/kg/24 h for each kg >20
Sodium	6 mmol (5–13)		2–4 mmol [†]
Potassium	5 mmol (3–6)		2–3 mmol
Chloride	4 mmol (3–9)		2–3 mmol
Phosphate	(0.5–2.5) mmol		1–2 mmol

Data are from measurements in only a few children and adolescents (8–12). In any individual patient, actual losses may be less or greater than the ranges shown in Table 1.

Three methods for determining maintenance water requirements in children are commonly used: *the Holliday-Segar formula (13) (shown in Table 1), a simplified Holliday-Segar formula (Simplified method based on Holliday-Segar: <10 kg 4 mL/kg/h; 11–20 kg 40 + 2 mL/kg/h for each kg between 11 and 20; >20 kg 60 + 1 mL/kg/h for each kg >20), and a formula based on body surface area for children more than 10 kg (1500 mL/m²/24 h) (14).

†Maintenance electrolyte requirements in children are per 100 mL of maintenance IV fluid (14, 15).

Clinical manifestations of DKA

- Dehydration
- Tachypnea; deep, sighing (Kussmaul) respiration
- Nausea, vomiting, and abdominal pain that may mimic an acute abdominal condition
- Confusion, drowsiness, progressive obtundation and loss of consciousness

Table 2 shows the volume of maintenance and replacement fluid volumes (based on body weight and an assumption of 10% dehydration) according to Darrow (16).

Definition of diabetic ketoacidosis (DKA)

The **biochemical criteria** for the diagnosis of DKA are (17):

- Hyperglycemia [BG >11 mmol/L (≈200 mg/dL)]
- Venous pH < 7.3 or bicarbonate <15 mmol/L
- Ketonemia* and ketonuria.

*Although not universally available, blood β-hydroxybutyrate (BOHB) concentration should be measured whenever possible; a level ≥3 mmol/L is indicative of DKA (18).

Urine ketones are typically ≥2+ ('moderate or large') positive. Partially treated children and children who have consumed little or no carbohydrate may rarely have only modestly elevated BG concentrations, referred to as 'euglycemic ketoacidosis' (19, 20).

Type 2 diabetes mellitus in the pediatric age range is increasing in frequency. The worldwide incidence and prevalence of type 2 diabetes in children and adolescents vary substantially among countries, age categories and ethnic groups, which can be explained by variations in population characteristics

and methodological dissimilarities between studies (21). At some centers in the USA, type 2 diabetes now accounts for up to one half of newly diagnosed diabetes in children aged 10–21 yr (22). The SEARCH for Diabetes in Youth Study in the USA found that nearly 10% of youth with type 2 diabetes presented with DKA (23); however, overall, 5–25% of patients with type 2 diabetes have DKA at the time of diagnosis (24).

The **severity of DKA** is categorized by the degree of acidosis (25):

- Mild: venous pH < 7.3 or bicarbonate <15 mmol/L
- Moderate: pH < 7.2, bicarbonate <10 mmol/L
- Severe: pH < 7.1, bicarbonate <5 mmol/L.

HHS, formerly referred to as hyperosmolar non-ketotic coma, may occur in young patients with type 2 diabetes (26–28), in type 1 diabetes subjects (29) and in infants, especially those with 6q24-related transient neonatal diabetes mellitus (30). **The criteria for HHS** include (31, 32):

- Plasma glucose concentration >33.3 mmol/L (600 mg/dL)
- Arterial pH > 7.30; venous pH > 7.25
- Serum bicarbonate >15 mmol/L
- Small ketonuria, absent to small ketonemia¹
- Effective serum osmolality >320 mOsm/kg
- Obtundation, combativeness, or seizures (in approximately 50%).

It is important to recognize that the overlap between the characteristic features of HHS and DKA may occur, and some patients with HHS, especially when there is severe dehydration, have mild or moderate acidosis that is mainly due

¹Nitroprusside reaction method.

Table 2. An alternative example of fluid volumes for the subsequent phase of rehydration

Body weight, kg	Maintenance mL/24 h	DKA: give maintenance + 5% of body weight/24 h	
		mL/24 h	mL/h
4	325	530	22
5	405	650	27
6	485	790	33
7	570	920	38
8	640	1040	43
9	710	1160	48
10	780	1280	53
11	840	1390	58
12	890	1490	62
13	940	1590	66
14	990	1690	70
15	1030	1780	74
16	1070	1870	78
17	1120	1970	82
18	1150	2050	85
19	1190	2140	89
20	1230	2230	93
22	1300	2400	100
24	1360	2560	107
26	1430	2730	114
28	1490	2890	120
30	1560	3060	128
32	1620	3220	134
34	1680	3360	140
36	1730	3460	144
38	1790	3580	149
40	1850	3700	154
45	1980	3960	165
50	2100	4200	175
55	2210	4420	184
60	2320	4640	193
65	2410	4820	201
70	2500	5000	208
75	2590	5180	216
80	2690	5380	224

DKA, diabetic ketoacidosis.

After initial resuscitation, and assuming 10% dehydration, the total amount of fluid should be given over 48 h. Table 2 shows volumes for maintenance and rehydration per 24 h and per hour. Fluids given orally (when patient has improved) should be subtracted from the amount in the table. Table 2 is based on maintenance volumes according to Darrow (16). For body weights >32 kg, the volumes have been adjusted so as not to exceed twice the maintenance rate of fluid administration. Example: A 6-yr-old boy weighing 20 kg will receive 10 mL/kg (or 200 mL) in the first 1-2 h and thereafter 93 mL/h or a total volume of 2230 mL/24 h for 48 h.

to hypoperfusion/lactic acidosis. Conversely, some children with type 1 diabetes may have features of HHS (severe hyperglycemia) especially if high carbohydrate containing beverages have been used to quench thirst and replace urinary losses before diagnosis (6). Therapy must be appropriately modified to address the pathophysiology and particular biochemical disturbances of the individual patient (see below). See page 16 regarding specific therapy of HHS.

Frequency of DKA

At disease onset

There is wide geographic variation in the frequency of DKA at onset of diabetes; rates inversely correlate with the regional incidence of type 1 diabetes. Frequencies range from approximately 15–70% in Europe and North America (23, 33–38). DKA at diagnosis is more common in younger children (<2 yr of age), often the consequence of diagnostic error or delayed treatment (39–41), those from ethnic minority groups, and in children whose families do not have ready access to medical care for social or economic reasons (20, 23, 37, 39, 42, 43).

In children with established diabetes

The risk of DKA in established type 1 diabetes is 1–10% per patient per year (3, 44–48):

Risk is increased in (47):

- Children who omit insulin (46).
- Children with poor metabolic control or previous episodes of DKA.
- Gastroenteritis with persistent vomiting and inability to maintain hydration.
- Children with psychiatric disorders, including those with eating disorders.
- Children with difficult or unstable family circumstances (e.g., parental abuse).
- Peripubertal and adolescent girls.
- Children with limited access to medical services.
- Insulin pump therapy (as only rapid- or short-acting insulin is used in pumps, interruption of insulin delivery for any reason rapidly leads to insulin deficiency) (3, 49).

In recurrent DKA, insulin omission or failure to follow sick day or pump failure management guidelines accounts for almost all episodes.

Management of DKA (Figure 2)

Emergency assessment

Acute management should follow the general guidelines for PALS (50, 51), with particular attention to the following aspects for the child who presents in DKA.

- Immediately measure BG and blood BOHB (or urine ketone) concentrations with bedside meters. Perform a clinical evaluation to identify a possible infection.
 - Measurement of blood BOHB concentration with a point-of-care meter, if available, is useful to

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confirm ketoacidosis (≥ 3 mmol/L in children) (18) and to monitor the response to treatment (52–58).

- **Weigh** the patient. If body surface area is used for fluid therapy calculations, measure height or length to determine surface area. The current weight should be used for calculations and not the weight from a previous office visit or hospital record.
- **Assess severity of dehydration.**

- Estimation of the degree of dehydration is imprecise and generally shows only fair to moderate agreement among examiners (59–61). It should be based on a combination of physical signs. The three most useful individual signs for predicting 5% dehydration in young children aged 1 month to 5 yr are:

- Prolonged capillary refill time (normal capillary refill is ≤ 1.5 –2 s)
- Abnormal skin turgor ('tenting' or inelastic skin)
- Abnormal respiratory pattern (hyperpnea) (62).

- Other useful signs in assessing degree of dehydration include: dry mucus membranes, sunken eyes, absent tears, weak pulses, and cool extremities. More signs of dehydration tend to be associated with more severe dehydration (62).

- $\geq 10\%$ dehydration is suggested by the presence of weak or impalpable peripheral pulses, hypotension, and oliguria.

- **Assess level of consciousness** [Glasgow coma scale (GCS) – see Table 3] (63).
- Obtain a **blood sample for laboratory measurement** of:

- Serum or plasma glucose
- Electrolytes (including bicarbonate)
- Blood urea nitrogen, creatinine
- Serum osmolality
- Venous pH, pCO₂
- Hemoglobin, hematocrit and complete blood count. Note that an increased white blood cell count in response to stress is characteristic of DKA and is not indicative of infection (64)
- Albumin, calcium, phosphorus, magnesium concentrations (if possible).

- Although not essential for management of DKA *per se*, hemoglobin A1c (HbA1c) may be useful in the evaluation and management of specific patients as it provides information about the duration of hyperglycemia.

- Perform a **urinalysis** for ketones.

- Obtain appropriate **specimens for culture** (blood, urine, and throat), only if there is evidence of infection (e.g., fever).

- If laboratory measurement of serum potassium is delayed, perform an **electrocardiogram (ECG)** for baseline evaluation of potassium status (65, 66).

Additional measures

For the pediatric patient who presents with a hyperglycemic crisis, the following aspects of emergency care warrant particular attention:

- **Secure the airway** and empty the stomach by continuous nasogastric suction to prevent pulmonary aspiration in the unconscious or severely obtunded patient.

Table 3. Glasgow coma scale or score (GCS)

Best eye response	Best verbal response	Best verbal response (non-verbal children)	Best motor response
1. No eye opening	1. No verbal response	1. No response	1. No motor response
2. Eyes open to pain	2. No words, only incomprehensible sounds; moaning	2. Inconsolable, irritable, restless, cries	2. Extension to pain (decerebrate posture)
3. Eyes open to verbal command	3. Words, but incoherent*	3. Inconsistently consolable and moans; makes vocal sounds	3. Flexion to pain (decorticate posture)
4. Eyes open spontaneously	4. Confused, disoriented conversation†	4. Consolable when crying and interacts inappropriately	4. Withdrawal from pain
	5. Oriented, normal conversation	5. Smiles, oriented to sound, follows objects and interacts	5. Localizes pain
			6. Obeys commands

The GCS consists of three parameters and is scored between 3 and 15; 3 being the worst and 15 the best (63). One of the components of the GCS is the best verbal response, which cannot be assessed in non-verbal young children. A modification of the GCS was created for children too young to talk.

*Inappropriate words, random or exclamatory articulated speech, but no sustained conversational exchange.

†Attention can be held; patient responds to questions coherently, but there is some disorientation and confusion.

- Intubation should be avoided if possible; a sudden increase of pCO₂ during or following intubation may cause cerebrospinal fluid (CSF) pH to decrease and contribute to worsening of cerebral edema (67).
- If there is a history of recent large consumption of glucose-containing fluids, consider emptying the stomach even in the patient who is not obtunded.
 - When large quantities of fruit juice or sweetened soft drinks have been ingested, the stomach may contain a large volume of water with little sodium. Gastric emptying early in the course of therapy leads to absorption of glucose and electrolyte-free water from the intestinal tract (7, 68).
- Give **oxygen** to patients with severe circulatory impairment or shock.
- A **cardiac monitor** should be used for continuous electrocardiographic monitoring to assess T waves for evidence of hyper- or hypokalemia (65, 66).
- A second **peripheral intravenous (IV) catheter** should be placed for convenient and painless repetitive blood sampling. An **arterial catheter** may, rarely, be necessary in some critically ill patients managed in an intensive care unit.
 - Unless absolutely necessary, avoid placing a central venous catheter because of the high risk of thrombosis, especially in the very young; if a central catheter has been inserted, remove it as soon as the patient's clinical status permits (69, 70).
 - Insulin should preferably not be given through a central line unless it is the only available option because its infusion may be interrupted when other fluids are given through the same line.
- Give **antibiotics** to **febrile patients** after obtaining appropriate cultures of body fluids.
- Catheterization of the bladder usually is not necessary, but if the child is unconscious or unable to void on demand (e.g., infants and very ill young children) the bladder should be catheterized.

Where should the child with DKA be managed?

The child should receive care in a unit that has:

- Experienced nursing staff trained in monitoring and management of DKA in children and adolescents.
- Written guidelines for DKA management in children.
- Access to a laboratory that can provide frequent and timely measurements of biochemical variables.

Whenever possible, a specialist/consultant pediatrician with training and expertise in the management of DKA should direct inpatient management. Where geographic constraints require that management be initiated in a center with less experience and with fewer resources, there should be arrangements in place for telephone or videoconference support from a physician with expertise in DKA.

Children with severe DKA (long duration of symptoms, compromised circulation, or depressed level of consciousness) or those who are at increased risk of cerebral edema (e.g., <5 yr of age, severe acidosis, low pCO₂, high blood urea nitrogen) should be considered for immediate treatment in an intensive care unit (pediatric if available) or in a unit that has equivalent resources and supervision, such as a children's ward specializing in diabetes care (17, 71).

In a child with **established diabetes**, whose parents have been trained in sick day management, hyperglycemia and ketosis without vomiting or severe dehydration can be managed at home or in an outpatient health care facility (e.g., emergency ward), provided an experienced diabetes team supervises the care (25, 72, 73).

Clinical and biochemical monitoring

Successful management of DKA and HHS requires **meticulous monitoring** of the patient's clinical and biochemical response to treatment so that timely adjustments in treatment can be made when indicated by the patient's clinical or laboratory data.

There should be documentation on a **flow chart** of hour-by-hour clinical observations, IV and oral medications, fluids, and laboratory results. Monitoring should include the following:

- Hourly (or more frequently as indicated) **vital signs** (heart rate, respiratory rate, blood pressure).
- Hourly (or more frequently as indicated) **neurological observations** (GCS; Table 3) for warning signs and symptoms of cerebral edema (see below).
 - Headache
 - Inappropriate slowing of heart rate
 - Recurrence of vomiting
 - Change in neurological status (restlessness, irritability, increased drowsiness, incontinence) or specific neurologic signs (e.g., cranial nerve palsies, abnormal pupillary responses)
 - Rising blood pressure
 - Decreased oxygen saturation
 - Rapidly increasing serum sodium concentration suggesting loss of urinary free water as a manifestation of diabetes insipidus (from

interruption of blood flow to the pituitary gland due to cerebral herniation).

- Amount of administered insulin.
- Hourly (or more frequently as indicated) accurate **fluid input** (including all oral fluid) **and output**.
- **Capillary blood glucose** concentration should be measured hourly (but must be cross-checked against laboratory venous glucose, as capillary methods may be inaccurate in the presence of poor peripheral circulation and acidosis).
- **Laboratory tests:** serum electrolytes, glucose, blood urea nitrogen, calcium, magnesium, phosphorus, hematocrit, and blood gases should be repeated 2–4 h, or more frequently, as clinically indicated, in more severe cases.
- Blood **BOHB** concentrations, if available, every 2 h (53–57).
 - Near-patient (also referred to as point-of-care) **BOHB** measurements correlate well with a reference method up to 3 mmol/L, but are not accurate above 5 mmol/L (55, 74).
- Lipids and triglycerides can be grossly elevated causing the blood sample to show a visible rim of lipids (75).
- If the laboratory cannot provide timely results, a portable biochemical analyzer that measures serum electrolytes and blood gases on fingerstick blood samples at the bedside is a useful adjunct to laboratory-based determinations. **BG** and blood or urine ketone concentrations can be measured with a bedside meter while awaiting results from the laboratory.
- **Calculations:**
 - Anion gap = $\text{Na} - (\text{Cl} + \text{HCO}_3)$: normal is 12 ± 2 mmol/L.
 - In **DKA**, the anion gap is typically 20–30 mmol/L; an anion gap >35 mmol/L suggests concomitant lactic acidosis.
 - Corrected sodium = measured Na + $2 \left[\frac{\text{plasma glucose} - 5.6}{5.6} \right]$ mmol/L or measured Na + $2 \left[\frac{\text{plasma glucose} - 100}{100} \right]$ mg/dL.
 - Effective osmolality (mOsm/kg) = $2 \times (\text{plasma Na}) + \text{plasma glucose mmol/L}$ (76).

Goals of therapy

- Correct dehydration
- Correct acidosis and reverse ketosis
- Restore **BG** to near normal
- Monitor for complications of **DKA** and its treatment
- Identify and treat any precipitating event

Fluids and salt

Patients with **DKA** have a deficit in **ECF** volume that usually is in the range of 5–10% (8, 9). Shock with hemodynamic compromise is rare in pediatric **DKA**. Clinical estimates of the volume deficit are subjective and inaccurate (59–61); therefore, in moderate **DKA** use 5–7% and in severe **DKA** 7–10% dehydration. The effective osmolality (formula above) is frequently in the range of 300–350 mmol/kg. Increased serum urea nitrogen and hematocrit or hemoglobin concentration or, alternatively, plasma albumin or total protein concentration if anemia is suspected (77) are useful markers of the degree of **ECF** contraction (73, 78, 79), and should be determined frequently during fluid resuscitation and deficit replacement (80). The serum sodium concentration is an unreliable measure of the degree of **ECF** contraction for two reasons: (i) glucose, largely restricted to the extracellular space, causes osmotic movement of water into the extracellular space thereby causing dilutional hyponatremia (81, 82) and (ii) the low sodium content of the elevated lipid fraction of the serum in **DKA**. The latter is not a concern with most modern methods for measuring sodium. It is useful to calculate the corrected sodium (using the above formula), which represents the expected sodium concentration in the absence of hyperglycemia, and monitor its changes throughout the course of therapy. As the plasma glucose concentration decreases after administering fluid and insulin, the measured serum sodium concentration should increase and the glucose-corrected sodium concentration (formula above) should slowly decrease. It is important to appreciate that the increase in measured serum sodium concentration does not indicate a worsening of the hypertonic state. A failure of measured serum sodium levels to rise or a further decline in serum sodium levels with therapy is thought to be a potentially ominous sign of impending cerebral edema (83–85). Too rapid and ongoing rise in serum sodium concentration may also indicate possible cerebral edema as a result of loss of free water in the urine from diabetes insipidus.

The objectives of fluid and electrolyte replacement therapy are:

- Restoration of circulating volume
- Replacement of sodium and the **ECF** and intracellular fluid deficit of water
- Improved glomerular filtration with enhanced clearance of glucose and ketones from the blood.

Principles of water and salt replacement

Despite much effort to identify the cause of cerebral edema its pathogenesis is incompletely understood. There continues to be controversy concerning the

association between the rate of fluid or sodium administration used in the treatment of DKA and the development of cerebral edema (86–88). No treatment strategy can be definitively recommended as being superior to another based on current evidence (87). The principles described below were developed after a comprehensive review of the literature and were accepted and endorsed by a panel of expert physicians representing the Lawson Wilkins Pediatric Endocrine Society (LWPES), the European Society for Paediatric Endocrinology (ESPE), and the International Society for Pediatric and Adolescent Diabetes (ISPAD) (17, 89).

- Water and salt deficits must be replaced.
- IV or oral fluids that may have been given in another facility before assessment should be factored into calculation of deficit and repair.

- **Resuscitation fluids** For patients who are severely volume depleted but not in shock, volume expansion (resuscitation) should begin immediately with 0.9% saline to restore the peripheral circulation. The volume administered typically is 10–20 mL/kg over 1–2 h, and may need to be repeated until tissue perfusion is adequate.

- In the rare patient with DKA in shock, rapidly restore circulatory volume with isotonic saline in 20 mL/kg boluses infused as quickly as possible through a large bore cannula with reassessment after each bolus.
- Use crystalloid not colloid. There are no data to support the use of colloid in preference to crystalloid in the treatment of DKA.

- **Deficit replacement fluids**

Subsequent fluid management (deficit replacement) should be with an isotonic solution (0.9% saline, Ringer’s lactate or Plasmalyte) for at least 4–6 h (78, 83, 90–93).

- Patients with mild DKA usually do not have impaired peripheral circulation and, therefore, do not require a fluid bolus. Fluid therapy should begin with deficit replacement plus maintenance fluid requirements.

- All children will experience a decrease in vascular volume when plasma glucose concentrations fall during treatment. It is, therefore, essential to ensure that they receive sufficient fluid and salt to maintain adequate tissue perfusion.

- Deficit replacement after 4–6 h should be with a solution that has a tonicity $\geq 0.45\%$ saline with added potassium chloride, potassium phosphate,

or potassium acetate (see below under potassium replacement) (78, 83, 90, 94–96). The decision to change from an isotonic to a hypotonic solution will depend on the patient’s hydration status, serum sodium concentration, and osmolality.

- In addition to providing the usual daily maintenance fluid requirement, replace the estimated fluid deficit at an even rate over 48 h (17, 78, 97). Except for severely ill individuals, oral intake typically begins within 24 h (97). Although rehydration was planned to occur over 48 h, in a study of 635 episodes of DKA the mean time to correction of DKA and complete restoration of the circulation was 11.6 ± 6.2 h. At this point, any remaining deficits were replenished by oral intake once DKA resolved and patients were transitioned to subcutaneous (SC) insulin (97).
- As the severity of dehydration may be difficult to determine and frequently is under- or overestimated (59–61), infuse fluid each day at a rate that seldom exceeds 1.5–2 times the usual daily maintenance requirement based on age, weight, or body surface area (17). See Table 2 for examples of calculations.
- Satisfactory outcomes have been reported using an alternative simplified method: after an initial fluid bolus of 20 mL/kg of normal saline, 0.675% saline (3/4 normal saline, 115.5 mmol sodium) is infused at 2–2.5 times the usual maintenance rate of fluid administration regardless of the degree of dehydration, and decreased to 1–1.5 times the maintenance rate after 24 h, or earlier if acidosis resolved, until urine ketones are negative (95, 98).

- Clinical assessment of hydration status and calculated effective osmolality are valuable guides to fluid and electrolyte therapy. The aim is gradually to reduce serum effective osmolality to normal (80, 97, 99). There should be a concomitant increase in serum sodium concentration as the serum glucose concentration decreases (sodium should rise by 0.5 mmol/L for each 1 mmol/L decrease in glucose concentration).
- Urinary losses should not routinely be added to the calculation of replacement fluid, but this may be necessary in rare circumstances.
- The sodium content of the fluid should be increased if measured serum sodium concentration is low and does not rise appropriately as the plasma glucose concentration falls (83, 93, 99, 100).
- The use of large amounts of chloride-rich fluids (combined with preferential renal excretion of ketones over chloride) may be associated with the rapid development of hyperchloremia (101–103) (defined as a ratio of chloride:sodium $[\text{Cl}^-:\text{Na}^+]$

Diabetic ketoacidosis and hyperglycemic hyperosmolar state

>0.79 (104)) and hyperchloremic metabolic acidosis (96, 102, 105–107).

- The acidifying effect of chloride can mask recognition of resolution of ketoacidosis when total base deficit is used to monitor biochemical improvement (103).
- When hyperchloremia develops, a persisting base deficit or low bicarbonate concentration can be erroneously interpreted as being due to ongoing ketosis.
- To prevent this misinterpretation, measurement of bedside BOHB levels will prevent any confusion and can demonstrate that ketoacidosis has resolved. Hyperchloremic acidosis resolves spontaneously.
- Although the anion gap is useful to track resolution of ketosis, it has two limitations in this setting: it is unable to differentiate a mixed metabolic acidosis (hyperchloremic and ketotic), and the degree of hyperchloremic acidosis is not quantifiable.
- Normally the difference between the serum sodium and chloride concentrations is 30–35 mmol/L. To partition the chloride component of the base deficit, the following formula has been proposed to enable clinicians to track resolution of ketoacidosis at the bedside: Chloride-induced base deficit = (plasma sodium – plasma chloride – 32) (103).
- The chloride load can be reduced by not giving potassium as potassium chloride and by using fluids such as Ringer's lactate or Plasmalyte in which a portion of the chloride is replaced by lactate or acetate, respectively (108).

Insulin therapy

DKA is caused by a decrease in effective circulating insulin associated with increases in counterregulatory hormone concentrations. Although rehydration alone frequently causes a marked decrease in BG concentration (109, 110), insulin therapy is essential to restore normal cellular metabolism and to normalize BG concentration and suppress lipolysis and ketogenesis (111).

There is evidence that 'low dose' IV insulin administration is safe and effective (97, 98, 112).

- Start insulin infusion 1–2 h after starting fluid replacement therapy; i.e., after the patient has received initial volume expansion (88).
- Correction of insulin deficiency.
 - Dose: 0.05–0.1 unit/kg/h [e.g., one method is to dilute 50 units regular (soluble) insulin in 50 mL normal saline, 1 unit = 1 mL] (113–120)

- Route of administration IV
- An IV bolus should *not* be used at the start of therapy; it is unnecessary (119, 121), may increase the risk of cerebral edema (88, 99, 122), and can exacerbate hypokalemia.
- The dose of insulin should usually remain at 0.05–0.1 unit/kg/h at least until resolution of DKA (pH > 7.30, bicarbonate >15 mmol/L, BOHB <1 mmol/L, or closure of the anion gap), which invariably takes longer than normalization of BG concentrations (123).
- If the patient shows marked sensitivity to insulin (e.g., some young children with DKA, patients with HHS, and some older children with established diabetes), the dose may be decreased provided that metabolic acidosis continues to resolve. For example, if a young child is receiving 0.05 unit/kg/h, it may be necessary to reduce the insulin dose to 0.03 unit/kg/h to prevent hypoglycemia.
- Uncontrolled retrospective and observational studies have reported comparable efficacy and safety using 0.05 unit/kg/h (124, 125), and some pediatric centers routinely use this dose for treatment of DKA. There are no comparative randomized controlled trial data, however, and no evidence that the higher dose is harmful.
- Insulin has an aldosterone-like effect leading to increased urinary potassium excretion (126–130). High doses administered intravenously for a prolonged period of time may contribute to a decrease in serum potassium concentration due to increased urinary potassium excretion despite potassium administration.
 - Time on IV insulin infusion and dose of insulin should be minimized to avoid severe hypokalemia (131).
- During initial volume expansion, the plasma glucose concentration falls steeply (109). Thereafter, and after commencing insulin therapy, the plasma glucose concentration typically decreases at a rate of 2–5 mmol/L/h, depending on the timing and amount of glucose administration (113–116, 118, 119, 132).
- To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycemia, 5% glucose should be added to the IV fluid (e.g., 5% glucose added to 0.9 or 0.45% saline) when the plasma glucose falls to approximately 14–17 mmol/L (250–300 mg/dL), or sooner if the rate of fall is precipitous.
 - It may be necessary to use 10% or even 12.5% dextrose to prevent hypoglycemia while continuing to infuse insulin to correct the metabolic acidosis.

- If BG falls very rapidly (>5 mmol/L/h) after initial fluid expansion, consider adding glucose even before plasma glucose has decreased to 17 mmol/L (300 mg/dL).
- If biochemical parameters of DKA (pH, anion gap, BOHB concentration) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin; e.g., infection, errors in insulin preparation.
- In circumstances where continuous IV administration is not possible and in patients with uncomplicated DKA, hourly or 2-hourly SC or intramuscular (IM) administration of a short- or rapid-acting insulin analog (insulin lispro or insulin aspart) is safe and may be as effective as IV regular insulin infusion (132–136), but should not be used in patients whose peripheral circulation is impaired.
 - Initial dose SC: 0.3 unit/kg, followed 1 h later by SC insulin lispro or aspart at 0.1 unit/kg every hour, or 0.15–0.20 units/kg every 2 h.
 - If BG falls to <14 mmol/L (250 mg/dL) before DKA has resolved, reduce SC insulin lispro or aspart to 0.05 unit/kg per hour to keep BG ≈ 11 mmol/L (200 mg/dL) until resolution of DKA.

Potassium replacement

Children with DKA suffer total body potassium deficits in the order of 3–6 mmol/kg (8–12). The major loss of potassium is from the intracellular pool. Intracellular potassium is depleted because of transcellular shifts of this ion caused by hypertonicity (increased plasma osmolality causes solvent drag in which water and potassium are drawn out of cells) and glycogenolysis and proteolysis secondary to insulin deficiency cause potassium efflux from cells. Potassium is lost from the body due to vomiting and as a consequence of osmotic diuresis. Volume depletion causes secondary hyperaldosteronism, which promotes urinary potassium excretion. Thus, total body depletion of potassium occurs, but at presentation serum potassium levels may be normal, increased or decreased (137). Renal dysfunction, by enhancing hyperglycemia and reducing potassium excretion, contributes to hyperkalemia (137). Administration of insulin and the correction of acidosis drive potassium back into the cells, decreasing serum levels (138). The serum potassium concentration may decrease abruptly, predisposing the patient to cardiac arrhythmias.

Replacement therapy is required regardless of the serum potassium concentration, except if renal failure is present (139, 140).

- If the patient is hypokalemic, start potassium replacement *at the time of* initial volume expansion

and before starting insulin therapy. Otherwise, start replacing potassium *after* initial volume expansion and concurrent with starting insulin therapy. If the patient is hyperkalemic, *defer* potassium replacement therapy until urine output is documented.

- If immediate serum potassium measurements are unavailable, an ECG may help to determine whether the child has hyper- or hypokalemia (65, 66). Prolongation of the PR interval, T-wave flattening and inversion, ST depression, prominent U waves, and apparent long QT interval (due to fusion of the T and U waves) indicates hypokalemia. Tall, peaked, and symmetrical T waves and shortening of the QT interval are the signs of hyperkalemia.
- The starting potassium concentration in the infusate should be 40 mmol/L. Subsequent potassium replacement therapy should be based on serum potassium measurements.
 - If potassium is given with the initial rapid volume expansion, a concentration of 20 mmol/L should be used.
- Potassium phosphate may be used together with potassium chloride or acetate; e.g., 20 mmol/L potassium chloride and 20 mmol/L potassium phosphate or 20 mmol/L potassium phosphate and 20 mmol/L potassium acetate. Administration of potassium entirely as potassium chloride contributes to the risk of hyperchloremic metabolic acidosis, whereas administration entirely as potassium phosphate can result in hypocalcemia.
- Potassium replacement should continue throughout IV fluid therapy.
- The maximum recommended rate of IV potassium replacement is usually 0.5 mmol/kg/h.
- If hypokalemia persists despite a maximum rate of potassium replacement, then the rate of insulin infusion can be reduced.

Phosphate

Depletion of intracellular phosphate occurs in DKA and phosphate is lost as a result of osmotic diuresis (8–10). Plasma phosphate levels fall after starting treatment and this is exacerbated by insulin, which promotes entry of phosphate into cells (141–143). Total body phosphate depletion has been associated with a variety of metabolic disturbances (144–146). Clinically significant hypophosphatemia may occur if IV therapy without food intake is prolonged beyond 24 h (8–10).

- Prospective studies involving relatively small numbers of subjects and with limited statistical power

have not shown clinical benefit from phosphate replacement (147–152).

- Severe hypophosphatemia combined with phosphate depletion (i.e., when not solely due to intracellular phosphate translocation) is uncommon, but can have severe consequences. Manifestations depend on the severity and chronicity of the phosphate depletion; patients usually do not have symptoms until plasma phosphate is <1 mg/dL (0.32 mmol/L).
- Severe hypophosphatemia can occur during the treatment of DKA; however, symptoms are uncommon because the hypophosphatemia is usually acute and typically there is no antecedent chronic phosphate deficiency.
- Clinical manifestations of hypophosphatemia are largely due to intracellular phosphate depletion. Decreased intracellular ATP levels impair cellular functions that depend on energy-rich phosphate compounds, and a decrease in 2,3-diphosphoglycerate (DPG) levels increases the affinity of hemoglobin for oxygen and reduces oxygen release in tissues (152). Many organ systems can be affected (145, 153). Manifestations include:
 - Metabolic encephalopathy (irritability, paresthesias, confusion, seizures, coma); impaired myocardial contractility and respiratory failure due to weakness of the diaphragm; muscle dysfunction with proximal myopathy, dysphagia, and ileus; rare hematologic effects include hemolysis, decreased phagocytosis and granulocyte chemotaxis, defective clot retraction and thrombocytopenia. Acute hypophosphatemia in a patient with preexisting severe phosphate depletion can lead to rhabdomyolysis (145, 154, 155).
- Severe hypophosphatemia associated with any of the above symptoms should be treated (156, 157).
- Administration of phosphate may induce hypocalcemia (158, 159).
- Potassium phosphate salts may be safely used as an alternative to or combined with potassium chloride or acetate, provided that careful monitoring of serum calcium is performed to avoid hypocalcemia (158, 159).

Acidosis

Severe acidosis is reversible by fluid and insulin replacement; insulin stops further ketoacid production and allows ketoacids to be metabolized, which generates bicarbonate. Treatment of hypovolemia improves tissue perfusion and renal function, thereby increasing the excretion of organic acids.

Controlled trials have shown no clinical benefit from bicarbonate administration (160–163). Bicarbonate therapy may cause paradoxical CNS acidosis (164, 165) and rapid correction of acidosis with bicarbonate causes hypokalemia (164, 166, 167). Bicarbonate administration may be beneficial in the rare patient with life-threatening hyperkalemia (168).

- If bicarbonate is considered necessary, cautiously give 1–2 mmol/kg over 60 min.

Complications of therapy

- Inadequate rehydration
- Hypoglycemia
- Hypokalemia
- Hyperchloremic acidosis
- Cerebral edema

Introduction of oral fluids and transition to SC Insulin Injections

- Oral fluids should be introduced only when substantial clinical improvement has occurred (mild acidosis/ketosis may still be present).
 - Persistent ketonuria (measurement of urine ketones with test strips is based on the nitroprusside reaction, which measures acetoacetate and acetone) characteristically occurs for several hours after serum BOHB levels have returned to normal (53, 57).
 - Absence of ketonuria should *not* be used as an endpoint for determining resolution of DKA.
- When oral fluid is tolerated, IV fluid should be reduced accordingly so that the sum of IV and oral fluids does not exceed the calculated IV rate (i.e., not in excess of 1.5–2 times maintenance fluid rate). This fluid restriction should be applied for 48 h from admission (72 h if there is severe hyperosmolality at onset of treatment).
- When ketoacidosis has resolved, oral intake is tolerated, and the change to SC insulin is planned, the most convenient time to change to SC insulin is just before a mealtime.
- To prevent rebound hyperglycemia, the first SC injection should be given 15–30 min (with rapid-acting insulin) or 1–2 h (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed. With intermediate- or long-acting insulin, the overlap should be longer and the rate of IV insulin infusion gradually lowered. For example, for patients on a basal-bolus insulin regimen, the first dose of basal insulin may be administered in the evening and the insulin infusion is stopped the next morning.

- The dose and type of SC insulin should be according to local preferences and circumstances.
- After transitioning to SC insulin, frequent BG monitoring is required to avoid marked hyperglycemia and hypoglycemia.

Morbidity and mortality

In population studies, the mortality rate from DKA in children is 0.15–0.30% (169–171) and may be decreasing (171). Cerebral injury is the major cause of mortality and morbidity (170, 172). Cerebral edema accounts for 60–90% of all DKA deaths (85, 173). From 10–25% of survivors of cerebral edema have significant residual morbidity (85, 173, 174). Children without overt neurological symptoms during DKA treatment may have subtle evidence of brain injury, particularly memory deficits, after recovery from DKA (175).

Other rare causes of morbidity and mortality include:

- Hypokalemia*
- Hypocalcemia, hypomagnesemia
- Severe hypophosphatemia*
- Hypoglycemia
- Other central nervous system complications include dural sinus thrombosis, basilar artery thrombosis, intracranial hemorrhage, and cerebral infarction (176–178)
- Venous thrombosis (69, 70)*
- Pulmonary embolism*
- Sepsis
- Rhinocerebral or pulmonary mucormycosis (179)
- Aspiration pneumonia*
- Pulmonary edema*
- Adult respiratory distress syndrome (ARDS)
- Pneumothorax, pneumomediastinum, and SC emphysema (180)
- Rhabdomyolysis*
- Ischemic bowel necrosis
- Acute renal failure*
- Acute pancreatitis (181)*

*These complications, often with fatality, have been frequent in HHS [see (32)]. The pathophysiology and management of HHS are discussed below.

Cerebral edema

The incidence of clinically overt cerebral edema in national population studies is 0.5–0.9% and the mortality rate is 21–24% (85, 173, 174). Mental status abnormalities (GCS scores <14), however, occur in approximately 15% of children treated for DKA and are associated with evidence of cerebral edema on neuroimaging (182, 183). The complication is

rarely seen after adolescence. Neuroimaging studies have led to the appreciation that cerebral edema is not a rare phenomenon in children with DKA, but occurs frequently with varying severity (182, 184, 185). Clinically overt cerebral edema likely represents the most severe manifestation of a common phenomenon (186).

The cause of cerebral edema is controversial. Some have explained the pathogenesis as the result of rapid fluid administration with abrupt changes in serum osmolality (100, 187–190). More recent investigations, however, have found that dehydration and cerebral hypoperfusion may be associated with DKA-related cerebral injury (85, 191–193), which have led to the formulation of an alternative hypothesis; namely, that factors intrinsic to DKA may be the cause of brain injury, which could be worsened during treatment (194, 195). It is noteworthy that the degree of edema that develops during DKA correlates with the degree of dehydration and hyperventilation at presentation, but not with factors related to initial osmolality or osmotic changes during treatment (183). Disruption of the blood–brain-barrier has been found in cases of fatal cerebral edema associated with DKA (196, 197), which further supports the view that cerebral edema is not simply caused by a reduction in serum osmolality.

Demographic factors that have been associated with an increased risk of cerebral edema include:

- Younger age (198)
- New onset diabetes (170, 198)
- Longer duration of symptoms (199)

These risk associations may reflect the greater likelihood of severe DKA.

Epidemiological studies have identified several potential risk factors at diagnosis or during treatment of DKA. These include:

- Greater hypocapnia at presentation after adjusting for degree of acidosis (85, 183, 200).
- Increased serum urea nitrogen at presentation (85, 183).
- More severe acidosis at presentation (88, 201, 202).
- Bicarbonate treatment for correction of acidosis (85, 203).
- A marked early decrease in serum effective osmolality (99, 202).
- An attenuated rise in serum sodium concentration or an early fall in glucose-corrected sodium during therapy (83–85, 202).
- Greater volumes of fluid given in the first 4 h (88, 200, 202).
- Administration of insulin in the first hour of fluid treatment (88).

Diabetic ketoacidosis and hyperglycemic hyperosmolar state

Immediate assessment

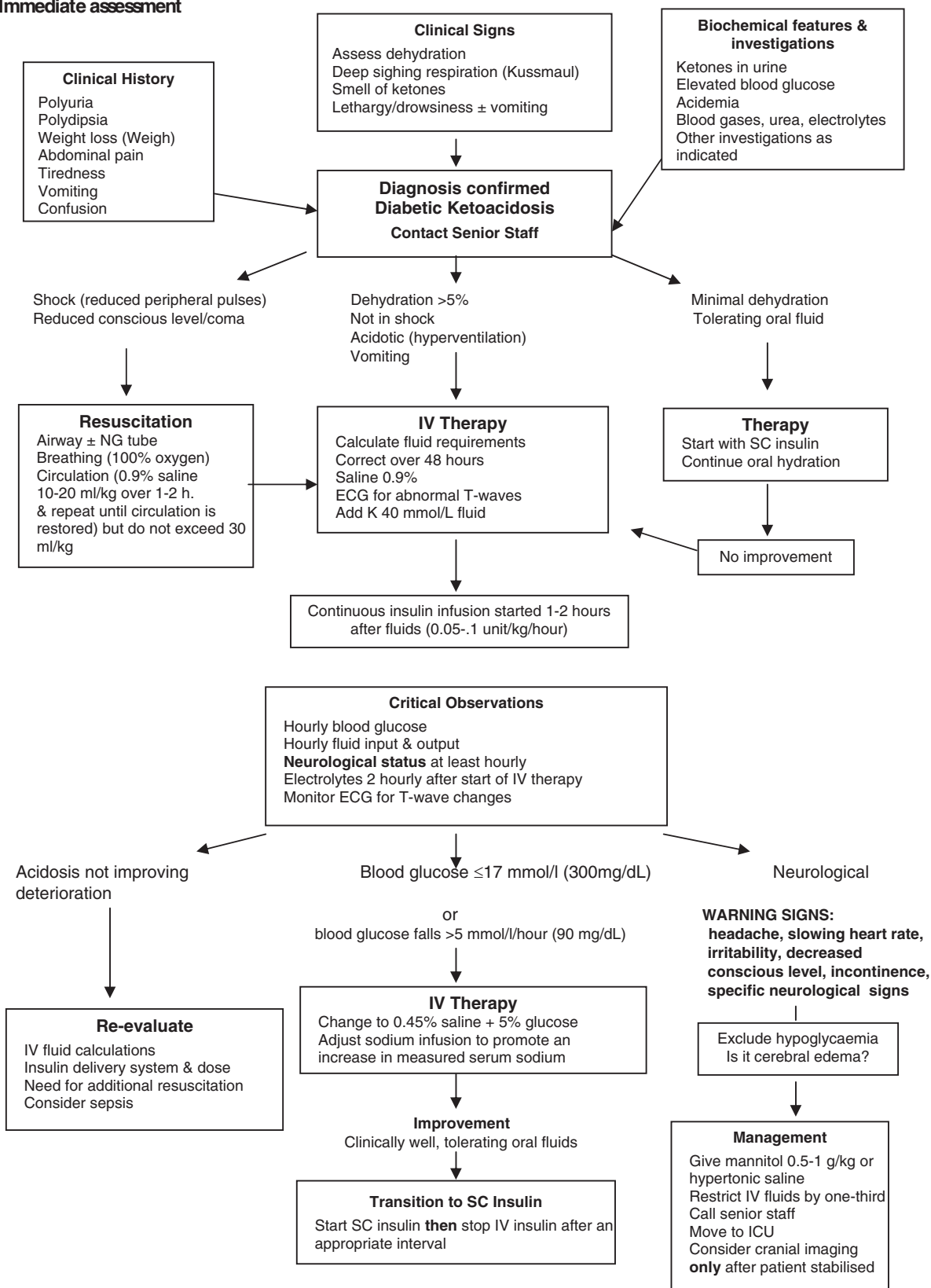


Fig. 2. Algorithm for the management of diabetic ketoacidosis. Adapted from Dunger et al. (233). NG, nasogastric; SC, subcutaneous.

Signs and symptoms of cerebral edema include:

- Headache and slowing of heart rate
- Change in neurological status (restlessness, irritability, increased drowsiness, and incontinence)
- Specific neurological signs (e.g., cranial nerve palsies, papilledema)
- Rising blood pressure
- Decreased O₂ saturation

Clinically significant cerebral edema usually develops within the first 12 h after treatment has started, but can occur before treatment has begun (85, 174, 204–207) or, rarely, may develop as late as 24–48 h after the start of treatment (85, 198, 208). Symptoms and signs are variable. Although mild to moderate headache at presentation may not be unusual (Glaser personal communication), development of a severe headache after treatment is always concerning. A method of clinical diagnosis based on bedside evaluation of neurological state is shown below (209). One diagnostic criterion, two major criteria, or one major and two minor criteria have a sensitivity of 92% and a false positive rate of only 4%. Signs that occur before treatment should not be considered in the diagnosis of cerebral edema.

Diagnostic criteria

- Abnormal motor or verbal response to pain
- Decorticate or decerebrate posture
- Cranial nerve palsy (especially III, IV, and VI)
- Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne–Stokes respiration, apneusis)

Major criteria

- Altered mentation/fluctuating level of consciousness
- Sustained heart rate deceleration (decrease more than 20 beats/min) not attributable to improved intravascular volume or sleep state
- Age-inappropriate incontinence

Minor criteria

- Vomiting
- Headache
- Lethargy or not easily arousable
- Diastolic blood pressure >90 mmHg
- Age <5 yr

A chart with the reference ranges for blood pressure and heart rate, which vary depending on height, weight, and gender, should be readily available, either in the patient’s chart or at the bedside.

The appearance of diabetes insipidus, manifested by increased urine output with a concomitant marked increase in the serum sodium concentration, reflecting loss of free water in the urine, is a sign of cerebral herniation causing interruption of blood flow to the pituitary gland.

Treatment of cerebral edema

- Initiate treatment as soon as the condition is suspected.
- Reduce the rate of fluid administration by one-third.
- Give mannitol, 0.5–1 g/kg IV over 10–15 min, and repeat if there is no initial response in 30 min to 2 h (210–212).
- Hypertonic saline (3%), suggested dose 2.5–5 mL/kg over 10–15 min, may be used as an alternative to mannitol, especially if there is no initial response to mannitol (213, 214).
 - A recent 11-yr retrospective cohort study showed that hypertonic saline has replaced mannitol as the most commonly used hyperosmolar agent in many US institutions. Although further investigation is needed, the data suggest that hypertonic saline may not have benefits over mannitol and may be associated with a higher mortality rate (171).
- Hyperosmolar agents should be readily available at the bedside.
- Elevate the head of the bed to 30°.
- Intubation may be necessary for the patient with impending respiratory failure.
- *After* treatment for cerebral edema has been started, cranial imaging may be considered as with any critically ill patient with encephalopathy or acute focal neurologic deficit. The primary concern is whether the patient has a lesion requiring emergency neurosurgery (e.g., intracranial hemorrhage) or a lesion that may necessitate anticoagulation (e.g., cerebrovascular thrombosis) (177, 215–217).

Hyperglycemic hyperosmolar state

This syndrome is characterized by extreme elevations in serum glucose concentrations and hyperosmolality without significant ketosis (32). Although the incidence of HHS is increasing (27, 28, 218), it is considerably less frequent in children than DKA.

Unlike the usual symptoms of DKA (hyperventilation, vomiting and abdominal pain), which typically bring children to medical attention, the gradually increasing polyuria and polydipsia of HHS may go unrecognized resulting in profound dehydration and

electrolyte losses. In adults, fluid losses in HHS have been estimated to be twice those of DKA; furthermore, obesity and hyperosmolality can make the clinical assessment of dehydration challenging. Despite severe volume depletion and electrolyte losses, hypertonicity preserves intravascular volume, and signs of dehydration may be less evident.

During therapy, decreasing serum osmolality (from enhanced glucosuria and insulin-mediated glucose uptake) results in the movement of water out of the intravascular space resulting in decreased intravascular volume, and osmotic diuresis may continue for hours in patients with extremely increased plasma glucose concentrations. Early in the course of treatment, urinary fluid losses may be considerable. As intravascular volume may decrease rapidly during treatment in patients with HHS, more aggressive replacement of intravascular volume (as compared to treatment of children with DKA) is required to avoid vascular collapse.

Treatment of HHS

There are no prospective data to guide treatment of children and adolescents with HHS. The following recommendations are based on extensive experience in adults and an appreciation of the pathophysiological differences between HHS and DKA (32); see Fig. 3. Patients should be admitted to an intensive care unit or comparable setting where expert medical, nursing, and laboratory services are available.

Fluid therapy

The goal of initial fluid therapy is to expand the intra- and extravascular volume and restore normal renal perfusion. The rate of fluid replacement should be more rapid than is recommended for DKA.

- The initial bolus should be ≥ 20 mL/kg of isotonic saline (0.9% NaCl) and a fluid deficit of approximately 12–15% of body weight should be assumed. Additional fluid boluses should be given, if necessary, to restore peripheral perfusion.
- Thereafter, 0.45–0.75% NaCl should be administered to replace the deficit over 24–48 h.
- The goal is to promote a gradual decline in serum sodium concentration and osmolality.
- ■ As isotonic fluids are more effective in maintaining circulatory volume, isotonic saline should be restarted if perfusion and hemodynamic status appear inadequate as serum osmolality declines.
- Serum sodium concentrations should be measured frequently and the sodium concentration in fluids adjusted to promote a gradual decline in corrected

serum sodium concentration. Mortality has been associated with failure of the corrected serum sodium concentration to decline with treatment, which may be an indication for hemodialysis. Hemodialysis has resulted in 80% survival in contrast to 20% with peritoneal dialysis (28).

- Although there are no data to indicate an optimal rate of decline in serum sodium, 0.5 mmol/L per hour has been recommended for hypernatremic dehydration (219). With adequate rehydration alone (i.e., before commencing insulin therapy), serum glucose concentrations should decrease by 75–100 mg/dL (4.1–5.5 mmol/L) per hour (220, 221).
- A more rapid rate of decline in serum glucose concentration is typical during the first several hours of treatment when an expanded vascular volume leads to improved renal perfusion. If there is a continued rapid fall in serum glucose (>90 mg/dL, 5 mmol/L per hour) after the first few hours, consider adding 2.5 or 5% glucose to the rehydration fluid. Failure of the expected decrease of plasma glucose concentration should prompt reassessment and evaluation of renal function.
- Unlike treatment of DKA, replacement of urinary losses is recommended (120). The typical urine sodium concentration during an osmotic diuresis approximates 0.45% saline; however, when there is concern about the adequacy of circulatory volume, urinary losses may be replaced with a fluid containing a higher sodium concentration.

Insulin therapy

Whereas tissue hypoperfusion in HHS commonly causes lactic acidosis, ketosis is usually minimal. Early insulin administration is unnecessary in HHS. Fluid administration alone causes a marked decline in serum glucose concentration as a result of dilution, improved renal perfusion leading to glucosuria, and increased tissue glucose uptake with improved circulation. The osmotic pressure that glucose exerts within the vascular space contributes to the maintenance of blood volume. A rapid fall in serum glucose concentration and osmolality after insulin administration may lead to circulatory compromise and thrombosis unless fluid replacement is adequate. Patients with HHS also have extreme potassium deficits; a rapid insulin-induced shift of potassium to the intracellular space can trigger an arrhythmia.

- Insulin administration should be initiated when serum glucose concentration is no longer declining at a rate of at least 50 mg/dL (3 mmol/L) per hour with fluid administration alone.

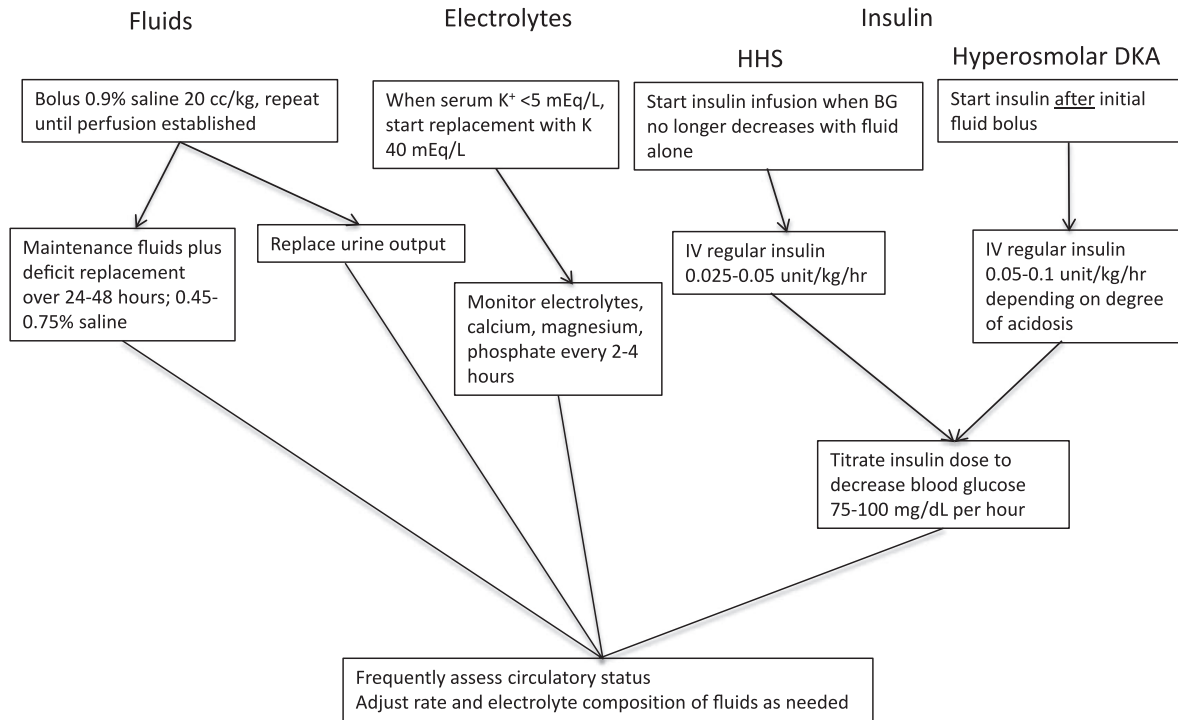


Fig. 3. Treatment of hyperglycemic hyperosmolar state (HHS). Adapted from Zeitler et al. (32).

- In patients with more severe ketosis and acidosis, however, insulin administration should be initiated earlier.
- Continuous administration of 0.025–0.05 units/kg/h can be used initially, with the dosage titrated to achieve a decrease in serum glucose concentration of 50–75 mg/dL (3–4 mmol/L) per hour.
 - Insulin boluses are not recommended.

Electrolytes

In general, deficits of potassium, phosphate, and magnesium are greater in HHS than DKA.

- Potassium replacement (40 mmol/L of replacement fluid) should begin as soon as serum potassium concentration is within the normal range and adequate renal function has been established.
 - Higher rates of potassium administration may be necessary after starting an insulin infusion.
 - Serum potassium concentrations should be monitored every 2–3 h along with ECG monitoring.
 - Hourly potassium measurements may be necessary if the patient has hypokalemia.
- Bicarbonate therapy is contraindicated; it increases the risk of hypokalemia and may adversely affect tissue oxygen delivery.

- Severe hypophosphatemia may lead to rhabdomyolysis, hemolytic uremia, muscle weakness, and paralysis. Although administration of phosphate is associated with a risk of hypocalcemia, an IV solution that contains a 50:50 mixture of potassium phosphate and another suitable potassium salt (potassium chloride or potassium acetate) generally permits adequate phosphate replacement while avoiding clinically significant hypocalcemia.
 - Serum phosphate concentrations should be measured every 3–4 h.
- Patients with HHS frequently have large magnesium deficits, but there are no data to determine whether the replacement of magnesium is beneficial.
 - Replacement of magnesium should be considered in the occasional patient who experiences severe hypomagnesemia and hypocalcemia during therapy. The recommended dose is 25–50 mg/kg per dose for 3–4 doses given every 4–6 h with a maximum infusion rate of 150 mg/min and 2 g/h.

Complications

- Venous thrombosis associated with the use of central venous catheters is a common hazard in HHS (69). Prophylactic use of low-dose heparin has been

suggested in adults but there are no data to indicate benefit from this practice. Heparin treatment should be reserved for children who require central venous catheters for physiologic monitoring or venous access and are immobile for more than 24–48 h (32). The central venous catheter should not be used for insulin administration because the large dead space may cause erratic insulin delivery.

- Rhabdomyolysis may occur in children with HHS resulting in acute kidney failure, severe hyperkalemia, hypocalcemia, and muscle swelling causing compartment syndrome (222). The classic symptom triad of rhabdomyolysis includes myalgia, weakness, and dark urine; monitoring creatine kinase concentrations every 2–3 h is recommended for early detection.
- For unknown reasons, several children with HHS have had clinical manifestations consistent with malignant hyperthermia, which is associated with a high mortality rate (26, 223–225). Patients who have a fever associated with a rise in creatine kinase concentrations may be treated with dantrolene, which reduces release of calcium from the sarcoplasmic reticulum and stabilizes calcium metabolism within muscle cells. Nonetheless, of the three reported patients with HHS reported to have been treated with dantrolene only one survived (223, 225).
- Altered mental status is common in adults whose serum osmolality exceeds 330 mOsm/kg; however, cerebral edema is rare (28). Among 96 cases of HHS reported in the literature as of 2010, including 32 deaths, there was only one instance of cerebral edema (Rosenbloom, personal communication). A decline in mental status after hyperosmolality has improved with treatment is unusual and should be promptly investigated.

Mixed HHS and DKA

Treatment must take into account potential complications of both DKA and HHS. Mental status must be closely monitored and frequent reassessment of circulatory status and fluid balance is necessary to guide therapy. To maintain an adequate circulatory volume, the rate of fluid and electrolyte administration usually exceeds that required for the typical case of DKA. Insulin is necessary to resolve ketosis and arrest hepatic gluconeogenesis; however, insulin infusion should be deferred until after the patient has received an initial fluid bolus and the circulation has been stabilized. Serum potassium and phosphate concentrations should be carefully monitored as described above for HHS.

Prevention of recurrent DKA

Management of an episode of DKA is not complete until its cause has been identified and an attempt made to treat it.

- Insulin omission, either inadvertently or deliberately, is the cause in most cases.
- The most common cause of DKA in insulin pump users is failure to take extra insulin with a pen or syringe when hyperglycemia and hyperketonemia or ketonuria occur.
- Home measurement of blood BOHB concentrations, when compared to urine ketone testing, decreases diabetes-related hospital visits (both emergency department visits and hospitalizations) by the early identification and treatment of ketosis (226). Blood BOHB measurements may be especially valuable to prevent DKA in patients who use a pump because interrupted insulin delivery rapidly leads to ketosis.
 - There may be dissociation between urine ketone (sodium nitroprusside only measures acetoacetate and acetone) and serum BOHB concentrations, which may be increased to levels consistent with DKA at a time when a urine ketone test is negative or shows only trace or small ketonuria (227).
- There usually is an important psychosocial reason for insulin omission.
 - An attempt to lose weight in an adolescent girl with an eating disorder.
 - A means of escaping an intolerable or abusive home situation.
 - Depression or other reason for inability of the patient to manage the diabetes unassisted.
- A psychiatric social worker or clinical psychologist should be consulted to identify the psychosocial reason(s) contributing to development of DKA.
- An infection is rarely the cause of DKA when the patient/family is properly educated in diabetes management and is receiving appropriate follow-up care by a diabetes team with a 24-h telephone helpline (228–230).
- Insulin omission can be prevented by comprehensive programs that provide education, psychosocial evaluation, and treatment combined with adult supervision of the entire process of insulin administration (231).
 - Parents and patients should learn how to recognize and treat ketosis and impending DKA with additional rapid- or short-acting insulin and oral fluids.

- Families should have access to a 24-h telephone helpline for emergency advice and treatment (228).
- When a responsible adult administers insulin there may be as much as a 10-fold reduction in frequency of recurrent DKA (231).

Conflicts of interest

The authors have declared no conflicts of interest.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Assessment and management of hypoglycemia in children and adolescents with diabetes

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- Hypoglycemia is the commonest acute complication of type 1 diabetes. Hypoglycemia may also occur in type 2 diabetes when treatment includes, for example, insulin or sulfonylurea therapy.
- The risk of hypoglycemia presents a major physiological and psychological barrier to achieving optimal glycemic control and may result in significant emotional morbidity for patients and carers.
- Monitoring hypoglycemia is a key component of diabetes care as is education about its causes, prevention, and treatment. Parents and caregivers need to be reassured that good glycemic control can be achieved without frequent severe hypoglycemic events.
- Hypoglycemia is best defined as a fall of the blood glucose level that exposes a patient to potential harm and there can be no single numerical definition of hypoglycemia for all patients and situations.

- A blood glucose level of <3.6 mmol/L (65 mg/dL) has been often accepted as a level for defining hypoglycemia. In clinical practice, however, a glucose value of ≤ 3.9 mmol/L (70 mg/dL) is used as the threshold value for initiating treatment for hypoglycemia in diabetes because of the potential for the glucose to fall further.
- In children, severe hypoglycemia is most often defined as an event associated with a seizure or loss of consciousness. In adults, an event requiring assistance from others is defined as severe but as almost all children require assistance with treatment, these events are more difficult to determine and events associated with significant neuroglycopenia may be classified as moderate events. All other hypoglycemic events are described as mild.
- Hypoglycemia is also classified as symptomatic and asymptomatic.
- The incidence of severe hypoglycemia varies with different surveys but most careful prospective studies

suggest a rate of 5 to 20/100 patient-years. This rate has fallen over the last 10 yr, but children remain at a higher risk than adults [B (1)].

- Symptoms of hypoglycemia in the young result from *adrenergic activation* (e.g., shakiness, pounding heart, and sweatiness) and *neuroglycopenia* (e.g., headache, drowsiness, and difficulty concentrating). In young children *behavioral* changes such as irritability, agitation, quietness, and tantrums may be prominent. The dominant symptoms may change with age.
- Symptoms of hypoglycemia and physiological hormone responses may occur at a higher glucose level in children compared to adults and thresholds for activation may be altered by chronic hyperglycemia (i.e., occur at a higher blood glucose) or repeated hypoglycemia (i.e., occur at a lower blood glucose level) (B).
- In type 1 diabetes, hypoglycemia results from imperfect insulin replacement. The risk of hypoglycemia is increased further by compromised counterregulatory hormone defects, including loss of the glucagon response to hypoglycemia, which may occur soon after diagnosis (B).
- Common clinical precipitants for hypoglycemia include: excessive insulin dosing, missed meals, exercise, sleep and, in adolescents, alcohol ingestion. Risk factors include young age, previous severe hypoglycemic events, and reduced hypoglycemia awareness. Lower A1C remains a risk factor but this association is less pronounced with contemporary therapy.
- Severe hypoglycemia requires urgent treatment. In a hospital setting, this may include intravenous glucose (10% glucose, 2–3 mL/kg) (B). In the home or ambulatory setting, intramuscular (IM) or subcutaneous (SC) glucagon should be given (<12 yr 0.5 mg, >12 yr 1.0 mg). Carers should receive training in its administration and have glucagon available (E).
- Milder hypoglycemic events should be treated with oral glucose (10 to 15 g glucose). Depending on the circumstances, rapid-acting glucose should be followed by additional carbohydrates to prevent recurrence of hypoglycemia (B).
- Exercise may be associated with hypoglycemia at the time of activity and up to 8 to 12 h later (delayed hypoglycemia) (B). Carers and patients should receive education and advice as to how to exercise safely and avoid hypoglycemic events.
- Sleep is a time of particular risk for severe hypoglycemia and asymptomatic hypoglycemia is common; because of this, routine testing is recommended overnight (B).
- Impaired hypoglycemia awareness occurs in children with diabetes and when present, is associated with a significantly increased risk of severe hypoglycemia.

The determination of hypoglycemia awareness should be a component of routine clinical review. Impaired awareness may be corrected by avoidance of hypoglycemia (B).

- New technologies including continuous glucose monitoring (CGM), closed-loop systems, and semi-closed loop systems offer potential to reduce the impact of hypoglycemia in the future (B).

Prevention of hypoglycemia

- Diabetes education is critical to preventing hypoglycemia.
- The aim of diabetes treatment should be to maintain blood glucose levels >3.9 mmol/L (70 mg/dL) while striving to achieve the best possible glycemetic control without the occurrence of severe hypoglycemia (A).
- Education about the risk factors for hypoglycemia should be given to patients and families to alert them as to times and situations when increased glucose monitoring is required and when treatment regimens need to be changed (E).
- Hypoglycemia should be prevented because its occurrence is frequently predictable, and it is often associated with significant psychosocial dysfunction; more importantly, it can in rare cases lead to permanent long-term sequelae and may be potentially life-threatening.
- Particular attention should be given to training children, parents, schoolteachers, and other caregivers to recognize the early warning signs of hypoglycemia and treat low blood glucose immediately and appropriately (E).
- Children and adolescents with diabetes should wear some form of identification or alert of their diabetes (E).
- An immediate source of glucose must always be available to young people with diabetes (A).
- Equipment for blood glucose measurement must be available to all children with diabetes for immediate confirmation and safe management of hypoglycemia (B, E).

Treatment of hypoglycemia

- Glucagon should be readily accessible to all parents and caregivers, especially when there is a high risk of severe hypoglycemia. Education on administration of glucagon is essential (E).
- Treatment of hypoglycemia should increase the blood glucose approximately 3–4 mmol/L (54–70 mg/dL). This can be accomplished by giving glucose tablets or sweetened fluids such as juice. Approximately 9 g of glucose is needed for a 30 kg

child and 15 g for a 50 kg child (approximately 0.3 g/kg).

- Following initial hypoglycemia treatment, blood glucose should be retested in 10–15 min. If there is no response or an inadequate response, repeat hypoglycemia treatment. Retest the blood glucose in another 10–15 min to confirm that target glucose (100 mg/dL) has been reached (E).
- Blood glucose monitoring should be performed prior to exercise, and extra carbohydrates should be consumed based on the blood glucose level and the expected intensity and duration of the exercise (B).
- Patients and their parents should be trained to contact their diabetes care provider if hypoglycemia is documented without symptoms or if the symptoms are those of neuroglycopenia and not autonomic symptoms (i.e., hypoglycemia unawareness).
- Blood glucose goals may need to be adjusted upward in patients with recurrent hypoglycemia and/or hypoglycemia unawareness (B).
- If unexplained hypoglycemia is frequent, evaluation for unrecognized celiac and Addison's disease should be considered (E).

Introduction

Hypoglycemia is the most common acute complication of type 1 diabetes (2, 3). The risk of recurrent and severe hypoglycemia causes significant anxiety and emotional morbidity for patients and families and is a limiting factor in achieving optimal glycemic control (4). For the child with type 1 diabetes, hypoglycemia can have a range of adverse consequences including unpleasant or embarrassing and potentially dangerous symptoms, impaired concentration, and behavioral disturbances. Severe, prolonged hypoglycemia, in particular during sleep, can result in coma, seizures, and even death (5, 6).

It is important that hypoglycemia is recognized as a key component of diabetes care and that patients and families receive education about its causes, effects, treatment, and prevention. At the same time, patients and families need reassurance that good glycemic control can be achieved without frequent severe hypoglycemic events as fear of hypoglycemia is common and disabling for many caregivers and young people with diabetes. Rates of severe hypoglycemia should be monitored as an important outcome of clinical management.

In recent years, there have been improvements in insulin therapy, including availability of insulin analogs, insulin pump therapy, and the introduction of CGM systems. Although there are some data to suggest that severe hypoglycemia has reduced in incidence recently (7, 8), hypoglycemia remains common (3). Furthermore, despite advances in therapy, the majority

of patients, particularly children, fail to achieve recommended glycemic targets in part because of the risk of hypoglycemic events (9, 10).

Definition and incidence

Definition

There is no consistent or agreed upon numerical definition of hypoglycemia for the child with diabetes.

Hypoglycemia is not defined by a single glucose value as glycemic thresholds for symptoms, central nervous system dysfunction, and hormonal counter-regulation vary both between individuals and in the same individual over time (11, 12). The American Diabetes Association and Endocrine Society work-group report (13) defines iatrogenic hypoglycemia in patients with diabetes as all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm. Blood glucose values of <3.3–3.9 mmol/L (60–70 mg/dL) are generally agreed to place the individual at risk of severe hypoglycemia because values in this range are associated with alterations in the counterregulatory hormones essential to the spontaneous reversal of hypoglycemia (11–13). A plasma concentration of ≤ 3.9 mmol/L (70 mg/dL) can be used as the threshold value for identifying and treating hypoglycemia in children with diabetes because of the potential for glucose levels to drop further. On the other hand, in clinical practice, the glucose value of <3.6 mmol/L (65 mg/dL) has been most often accepted as a level for defining hypoglycemia.

Severe hypoglycemia

In the adult population, severe hypoglycemia is defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions (13). In childhood, this definition is problematic as most young children require assistance to correct even mild hypoglycemia. As a result, in the pediatric population, severe hypoglycemia is generally defined as an event associated with severe neuroglycopenia usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose) (14).

Mild/moderate hypoglycemia

There is no clinically important reason to distinguish between mild and moderate hypoglycemia, and younger children will almost always need to be treated by a parent or caregiver. For this reason, mild and moderate hypoglycemia are considered together.

Symptomatic hypoglycemia occurs when the child or parent is aware of, responds to, and treats the hypoglycemia orally after documenting a blood glucose level of ≤ 3.9 mmol/L (70 mg/dL).

Asymptomatic hypoglycemia applies when the child is not symptomatic with hypoglycemia but the blood glucose is documented to be ≤ 3.9 mmol/L (70 mg/dL). It is important to consider asymptomatic hypoglycemia, especially if ≤ 3.6 mmol/L (65 mg/dL), in order to recognize the frequency of hypoglycemia unawareness or glucose values that place an individual at risk for hypoglycemia unawareness.

Incidence

The incidence of moderate or mild hypoglycemia is unknown. Such events occur frequently among patients treated with insulin and are quite often unrecognized or underreported. Severe hypoglycemia is more likely to be recognized. Variations in definitions, sample sizes, and retrospective surveys have made comparisons between studies difficult.

Among adolescents participating in the Diabetes Control and Complications Trial (DCCT), the incidence of hypoglycemia requiring treatment assistance was 86/100 patient-years in intensively treated vs. 28/100 patient-years in those conventionally treated (15). The incidence of coma or seizure in these adolescents was 27/100 patient-years and 10/100 patient-years, respectively.

Several studies have examined the incidence rates of severe hypoglycemia in children during post-DCCT era. Few studies used a prospective design or were population-based. The incidence of severe hypoglycemia of 19/100 patient-years was reported from a large cohort of children with type 1 diabetes aged 0–19 yr followed by the Barbara Davis Center for Childhood Diabetes, Denver, CO, USA (16).

More recently, there is emerging evidence that rates of severe hypoglycemia may be declining. Data from the T1D Exchange, a registry of >25 000 individuals with type 1 diabetes at 67 centers in the USA (17), reported a 12-month frequency of 6.2% of one or more severe hypoglycemia events with seizure or loss of consciousness in their 2 to 26-yr-old cohort. This compares to a prevalence of severe hypoglycemia of 27% over a 4 yr period in the earlier Denver cohort (16).

O'Connell et al. (7) recently reported one of the largest studies monitoring the epidemiology of severe hypoglycemia in children with type 1 diabetes in Australia. The rate of severe hypoglycemia per 100 patient-years peaked at 17.3 in 2001 and then declined from 2004 to a nadir of 5.8 in 2006. The reduction in the hypoglycemia rate may have resulted from changes in clinical practice including new insulin regimens, more intensive glucose monitoring, improved management guidelines, but this remains speculative. In contrast to previous studies from the same center (18), in this cohort, an A1C <7% was not significantly associated with higher risk of severe hypoglycemia, compared

with the reference group of A1C 8–9%, which was the average level in this cohort across the decade. Children with duration of diabetes >1 yr had a significantly higher risk than those with duration of diabetes <1 yr. In adolescents, pump therapy was associated with a reduced incidence of severe hypoglycemia.

Signs and symptoms

Hypoglycemia is often accompanied by signs and symptoms of autonomic (adrenergic) activation and/or neurological dysfunction from glucose deprivation in the brain (neuroglycopenia) (19), as shown in Table 1. As the blood glucose falls, the initial symptoms result from activation of the autonomic nervous system and include shakiness, weakness, hunger, and sweating. These symptoms occur at a blood glucose level of approximately 3.2–3.6 mmol/L (58–65 mg/dL) in children without diabetes, which is higher than in adults (11). A third group of symptoms including behavioral changes such as tantrums, may be described in younger children. Chronic hyperglycemia and poor glycemic control can result in an adaptive shift of the threshold of onset for these hypoglycemic symptoms to a higher glucose level, which at times falls in the euglycemic range (20). Neuroglycopenic symptoms result from brain glucose deprivation and include headache, difficulty concentrating, blurred vision, difficulty hearing, slurred speech, and confusion. Behavioral changes such as irritability, agitation, quietness, stubbornness, and tantrums may be the prominent symptom particularly for the preschool child, and may result from a combination of neuroglycopenic and autonomic responses (21).

In this younger age group, observed signs are more important, and at all ages there is a difference between reported and observed symptoms or signs. The dominant symptoms of hypoglycemia tend to differ depending on age, with neuroglycopenia more common than autonomic symptoms in the young (22).

Physiological responses in children and adolescents

It is now well recognized that although many physiological responses are similar across the age groups, there can be significant developmental and age-related differences in children and adolescents. The DCCT demonstrated a higher rate of severe hypoglycemic events in the adolescent subgroup compared with the adult cohort, 0.9 vs. 0.6 events requiring assistance per patient per year (15). This occurred in both adolescent and adult intensive and conventional therapy groups despite adolescents having poorer glycemic control with A1C levels approximately 1% higher. This difference in glycemic control at the time was associated with lower, not higher, rates of hypoglycemia.

Table 1. Hypoglycemia signs and symptoms

<i>Autonomic signs and symptoms</i>
Shakiness
Sweatiness
Trembling
Palpitations
Pallor
<i>Neuroglycopenic signs and symptoms</i>
Poor concentration
Blurred or double vision
Disturbed color vision
Difficulty hearing
Slurred speech
Poor judgment and confusion
Problems with short-term memory
Dizziness and unsteady gait
Loss of consciousness
Seizure
Death
<i>Behavioral signs and symptoms</i>
Irritability
Erratic behavior
Agitation
Nightmares
Inconsolable crying
<i>Non-specific symptoms</i>
Hunger
Headache
Nausea
Tiredness

There are a number of physiologic and behavioral mechanisms that contribute to this difference. Firstly, there are behavioral factors such as variable adherence that have been clearly associated with poor glycemic control in the adolescents (23). Secondly, during puberty, adolescents with or without type 1 diabetes are more insulin resistant than adults (24). Adolescents also have quantitative differences in counterregulatory hormone responses. During hypoglycemia, adolescents with or without diabetes release catecholamines, cortisol, and growth hormone at a higher glucose level than adults (11). There is some evidence that neuroglycopenia may develop at a higher glucose level in youth, suggesting a greater susceptibility to hypoglycemia in the young (11, 20).

To date, nearly all studies have been conducted in adolescents and as a result less is known about responses in preadolescents, whether younger children demonstrate a similar or different effect is unknown primarily as a result of the difficulty of studying this age group. The susceptibility of the brain to the adverse effects of severe hypoglycemia may differ with age and neurodevelopmental stage.

Treatment

Goal

The goal of hypoglycemia treatment is to restore the blood glucose level to euglycemia or to 5.6 mmol/L (100 mg/dL).

Severe hypoglycemia

In the event of severe hypoglycemia, urgent treatment is required. Severe hypoglycemia with loss of consciousness and/or convulsions when it occurs out of the hospital environment is most safely and rapidly reversed by injection of glucagon, 0.5 mg for age <12 yr, 1.0 mg for ages >12 yr, or 10–30 mcg/kg body weight (25). Glucagon is given intramuscularly or subcutaneously. Current available preparations require glucagon reconstitution with sterile water and therefore parents and caregivers require instruction on how to prepare and administer glucagon with frequent reminder education.

In a hospital setting, intravenous glucose or glucagon may be given. Intravenous glucose should be administered by trained personnel over several minutes to reverse hypoglycemia. The recommended dose is glucose 10–30%, for a total of 200–500 mg/kg of glucose (glucose 10% is 100 mg/mL). Rapid administration, or excessive concentration (i.e., glucose 50%) may result in an excessive rate of osmotic change and risk of cerebral edema.

When glucagon is not available, a common practice is to administer a rapid-acting source of glucose such as glucose gel or honey into the buccal pouch; however, the efficacy of this practice is anecdotal and there is no scientific evidence for absorption of the glucose from the buccal mucosa. In one study in adults, there was no buccal absorption of glucose (26). In many developing countries neither glucagon nor glucose gel may be available; often a powder form (glucose D 25 g) of glucose is used.

In the recovery phase after treatment of severe hypoglycemia, close observation and glucose monitoring is essential. Vomiting is common and recurrent hypoglycemia may occur. In the event of recurrent hypoglycemia, the child will require additional oral carbohydrates and/or intravenous infusion of glucose at a suggested dose of glucose 10%, 2–5 mg/kg/min (1.2–3.0 mL/kg/h). In the outpatient setting, the predisposing events that led to the severe event should be evaluated to allow for prevention of future events. Caregivers need to be aware that following a severe hypoglycemic event the child will be at significantly higher risk of a future event and alterations to therapy may be appropriate.

Mild/moderate hypoglycemia

If the blood glucose is 3.3–3.9 mmol/L (60–70 mg/dL) and the child does not experience uncomfortable symptoms, immediate intake of carbohydrates will raise the blood glucose sufficiently. In adults, 20 g of carbohydrate in the form of glucose tablets raised glucose levels by approximately 2.5–3.6 mmol/L

(45–65 mg/dL) (27–29). This has been extrapolated to 0.3 g/kg in children or approximately 9 g of glucose for a 30 kg child and 15 g for a 50 kg child. It is important, however, to remember that the amount of carbohydrate required will depend on the size of the child, type of insulin therapy, active insulin on board, the timing and intensity of antecedent exercise as well as other factors (27, 30).

The type of carbohydrate is also important as 40 g of carbohydrate in the form of juice was needed to give approximately the same rise as 20 g in the form of glucose tablets (27). Sucrose likewise requires a greater amount to provide the same increase in blood glucose compared to glucose (28). Milk containing 20 g of carbohydrate gave only a rise of approximately 1 mmol/L (18 mg/dL). Chocolate, milk, and other foods containing fat will cause the glucose to be absorbed more slowly and should be avoided as the initial treatment of hypoglycemia (27).

After treatment, retest blood glucose after 10–15 min. If there is no response or an inadequate response, repeat oral intake as above. For initially lower glucose values, as symptoms improve or euglycemia is restored, complex carbohydrates in the form of fruit, bread, cereal, or milk, may be ingested to prevent recurrence of hypoglycemia.

Risk factors

Ultimately, it is excessive insulin or excessive insulin action that causes hypoglycemia in the child with type 1 diabetes. A range of clinical factors associated with the occurrence of severe hypoglycemia in children and adolescents are shown in Table 2. Hypoglycemia occurs more frequently in younger children due to unpredictable food consumption, physical activity, and increased sensitivity to insulin, although recent data from the Type 1 Diabetes Exchange and the Diabetes Patienten Verlaufsdokumentation (DPV) registry did not find increased rates of severe hypoglycemia in those <6 yr of age with A1C <7.5% compared to those with A1C 7.5–8.5% or >8.5% (31). The relation between severe hypoglycemia and lower A1C has been extensively explored, especially in children. Alcohol suppresses gluconeogenesis and glycogenolysis and may induce hypoglycemia unawareness. In addition, alcohol ingestion acutely improves insulin sensitivity. In combination with exercise, alcohol consumption can lead to severe hypoglycemia, which may occur up to 10–12 h after exercise or alcohol ingestion.

Education about the risk factors for hypoglycemia should be given to patients and families to alert them to times and situations when increased glucose monitoring is required and when treatment regimens needs to be changed.

Table 2. Clinical factors associated with hypoglycemia

<i>Precipitants</i>
Excess insulin
Less food consumption
Exercise
Sleep
Alcohol ingestion
<i>Risk factors</i>
Younger age, <6 yr
Lower A1C levels
Hypoglycemia unawareness
Previous severe hypoglycemia
Longer duration of diabetes

The majority of children with type 1 diabetes who experience severe hypoglycemia have isolated events, however a small number suffer recurrent episodes. When hypoglycemia is recurrent, it is important to exclude coexisting autoimmune disorders such as thyroid disease, Addison's disease, and celiac disease. Impaired hypoglycemia awareness and hypoglycemia-associated autonomic failure (HAAF) (12) may develop in children and adolescents and should be considered in patients who experience recurrent hypoglycemia. Undisclosed self-administration of insulin is a recognized cause of repeated and unexplained severe hypoglycemia and should be considered as a sign of psychological distress (32).

The comorbidities of celiac disease, present in 4–10% of children with type 1 diabetes, and Addison's disease, present much less commonly (33), may also increase the risk for hypoglycemia (34, 35). The introduction of a gluten-free diet and appropriate treatment of Addison's disease may reduce the frequency of hypoglycemia (36, 37).

Exercise

Physical activity is an essential component of childhood play and sport, and offers physiological and psychological benefits for all age groups with type 1 diabetes. Unfortunately, exercise can increase the risk of hypoglycemia through various mechanisms. These are not well understood and include increased insulin absorption, increased insulin sensitivity, depletion of glucose stores, and exercise-induced counterregulatory hormone deficits. Hypoglycemic risk may be increased both at the time of exercise and also in the 24 h following activity (38).

Evidence suggests that blood glucose levels <6.7–8.3 mmol/L (120–150 mg/dL), prior to sustained aerobic exercise (75 min) in the afternoon, is associated with a high probability of hypoglycemia within 60–75 min (39). Discontinuing continuous insulin infusion therapy for up to 2 h during exercise may help to prevent exercise-related hypoglycemia (39).

During prolonged exercise, 15 g of carbohydrate will raise the blood glucose by approximately 1 mmol/L (18 mg/dL) for a 50 kg child (27), therefore, 30–45 g of oral carbohydrate may be required to prevent hypoglycemia for a 30 kg child and 50–75 g for 50 kg child. Additional carbohydrate will usually be required if exercise occurs at the peak of insulin action (39–41). Likewise carbohydrate requirement will be lower if the premeal bolus prior to the exercise is lowered or if the exercise occurs several hours after the last meal bolus has been given. In many individuals, a lowering of the insulin dose after intense exercise should be considered to prevent nocturnal hypoglycemia.

The management of hypoglycemia during and after exercise adds to the complexity of the diabetes treatment regimen. Recent research has enhanced our comprehension of the underlying mechanisms responsible for hypoglycemia after activity. A number of excellent reviews and treatment guidelines for physical activity in children with type 1 diabetes have been published recently (41, 42) and are updated in this edition of the ISPAD guidelines.

Nocturnal hypoglycemia

Nocturnal hypoglycemia causes significant anxiety and morbidity for the families of children with type 1 diabetes (43). This is in part because our understanding of nocturnal glucose homeostasis and etiology of nocturnal hypoglycemia is very limited. The counterregulatory responses to hypoglycemia are attenuated during sleep (44, 45) and patients with type 1 diabetes are much less likely to be awakened by hypoglycemia than individuals without diabetes (44). Recent studies have reported an alarmingly high prevalence of prolonged, nocturnal hypoglycemia, up to 40% on any given night in children and adolescents with type 1 diabetes (46–48). Almost half of these episodes are undetected by carers or individuals with diabetes (46, 49). A recent report from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring (JDRF-CGM) study group described frequent prolonged nocturnal hypoglycemia on 8.5% of nights in both children and adults but more prolonged in children (3). Such prolonged hypoglycemia may result in seizure and occasionally death. The same report reported that the median time spent in a hypoglycemia range approached 60 min/ d. Such frequent hypoglycemia is likely to contribute to counterregulatory deficit and increased risk of further hypoglycemia.

Nocturnal hypoglycemia should be suspected if prebreakfast blood glucose is low, and/or confusional states, nightmares, or seizures occur during the night, or if impaired thinking, lethargy, altered mood, or headaches are experienced on waking (14). It

is recommended that parents and patients monitor overnight glucose levels on a regular basis, particularly if there is an additional risk factor that may predispose to nocturnal hypoglycemia.

Studies of overnight hypoglycemia in children have been unable to identify a glucose value that reliably predicts a low risk of hypoglycemia. In a study using CGM to detect nocturnal hypoglycemia, there was a twofold increase, 45 vs. 22% in the incidence of hypoglycemia with a bedtime glucose ≤ 5.5 mmol/L (100 mg/dL) (48). Perhaps of greater value is the fasting glucose concentration, with values < 7 mmol/L (126 mg/dL) suggesting that hypoglycemia has occurred overnight (46, 47).

Studies of dietary intervention to prevent nocturnal hypoglycemia in adults with type 1 diabetes have found that a bedtime snack containing carbohydrate and protein offers some protection from nocturnal hypoglycemia, compared with carbohydrates alone (50). The beneficial effects of uncooked cornstarch have been variable in children (51, 52).

The occurrence of severe nocturnal hypoglycemia has been reduced by the use of insulin pump therapy (53). This effect is likely to result from the ability to finely adjust basal insulin delivery with the use of pump therapy. In a study of 23 children and adolescents in a randomized, crossover study comparing multiple daily injections to pump therapy, pump therapy was associated with a smaller area under the curve for nocturnal hypoglycemia (54). This same study also utilized CGM, which has been helpful in identifying the frequency and duration of nocturnal hypoglycemia (54, 55).

Brain dysfunction and neurological sequelae of hypoglycemia

The impact of type 1 diabetes on the developing brain remains controversial. Early onset of diabetes, before the age of 6 yr, has long been identified as one of the strongest risk factors associated with cognitive dysfunction, ranging from poorer performance on general intellectual testing (56) to specific deficits with visuospatial tasks, attention, and psychomotor efficiency. The effect of early-onset diabetes however, is confounded by the impact of recurrent severe hypoglycemia. Repeated severe hypoglycemia has been reported to adversely affect various cognitive domains, in particular long-term memory, attention, and verbal IQ, although results have been inconsistent across studies (57, 58). Moreover, a considerable limitation of many of these studies is the retrospective collection of hypoglycemia history.

A recent study reported the neurocognitive outcomes in 84 children with early-onset diagnosis of type 1 diabetes, defined as type 1 diabetes onset before 6 yr

of age (59). In an earlier study (58) by the same group, subjects with a history of early severe hypoglycemia were compared to those with a history of late severe hypoglycemia and also compared those that had experienced severe hypoglycemia to subjects with no history of seizures. Surprisingly, there were no group differences revealed on intellectual, memory, or behavioral measures. Furthermore, there was no evidence that episodes of seizure or coma, even those occurring in early childhood, resulted in broad cognitive dysfunction nor was there evidence of specific memory difficulties at the time of testing. In a follow-up study evaluating a subset of these children at the mean age of 19.3 yr, there was no difference in general intellectual ability, memory, and emotional difficulties in this cohort of young adults with early-onset type 1 diabetes compared to control subjects and no deterioration over time (59). There were however, findings to suggest subtle changes leading to poorer performance on complex tasks of executive function. Larger prospective studies are required to explore this issue further.

Despite these reassuring findings on cognitive function, brain abnormalities have been associated with severe hypoglycemia in other studies. Repeated episodes of hypoglycemic seizures in young children may cause structural changes, as evidenced by the prevalence of mesial temporal sclerosis in 16% of a cohort of children with early-onset type 1 diabetes (60). In a large sample of young patients with type 1 diabetes using voxel-based morphometry, regional brain volume differences were associated with both a history of hypoglycemia and hyperglycemia (61). A recent report from the DirecNet group reported significantly reduced axial diffusivity, a measure of white matter structure, in a large cohort of children with type 1 diabetes compared to aged-matched control subjects (62).

The role of early-onset diabetes and chronic hyperglycemia in the decrease of cognitive functioning in very young children has also received increased attention (63, 64). There is accumulating evidence that hyperglycemia in the young child may be an important factor resulting in abnormalities in brain structure and function (65–67).

Impaired hypoglycemia awareness

Impaired hypoglycemia awareness can be defined as the inability to perceive the onset of hypoglycemia, and in adults is associated with a resetting of the glycemic thresholds for the generation of symptoms, activation of counterregulatory hormonal secretion, and of cognitive impairment to lower levels of blood glucose. Typically, autonomic symptoms are lost before neuroglycopenic symptoms, which then predominate.

The threshold for autonomic symptoms may be affected by antecedent hypoglycemia. This may be accompanied by reduced intensity of symptoms following the hypoglycemic event, leading to impaired hypoglycemia awareness during this time (68). Moderate exercise one day may also result in a decrease in symptoms of hypoglycemia and decrease hormonal response the following day (69). The blood glucose threshold for cognitive dysfunction may then be triggered before autonomic activation. The blood glucose threshold for neuroglycopenia does not appear to vary as much with the level of glucose control nor with antecedent hypoglycemia (11, 70, 71). The blood glucose threshold for activation of autonomic symptoms is related to activation of counterregulatory hormones and has been shown to be higher in children than in adults and to vary directly with the level of blood glucose control, with a higher A1C associated with a higher blood glucose threshold (11, 72). This is important given that impaired hypoglycemia awareness is a major risk factor for severe hypoglycemia, accounting for 36% of the episodes of severe hypoglycemia that occurred in the DCCT while adult subjects were awake (73).

It is unclear whether an identical syndrome of impaired awareness of hypoglycemia develops in children and adolescents before puberty. In a series of 656 children with type 1 diabetes (74), impaired hypoglycemia awareness was reported in 30% of the population, which is consistent with adult studies with type 1 diabetes. In this study, impaired hypoglycemia awareness in children was associated with a threefold likelihood of having had a severe hypoglycemic event (coma or convulsion) in the preceding 12 months. An episode of antecedent hypoglycemia may reduce the symptomatic and autonomic response to subsequent hypoglycemia which in turn further increases the risk of subsequent severe hypoglycemia.

There is evidence that loss of hypoglycemia awareness can be reversed by avoiding hypoglycemia for 2–3 wk (75), but this may be very difficult to accomplish in young children. It is possible that the pathogenesis of impaired hypoglycemia awareness and the associated syndrome of counterregulatory hormone deficiency, is in young people similar to that described in adults, as attempts to restore symptomatic responses by strict avoidance of hypoglycemia with the use of real-time CGM, at least in preliminary studies, appear to be successful (76).

Current therapies

Continuous glucose monitoring systems

Data from large trials including the JDRF-CGM (3) and sensor-augmented pump therapy for A1C

Table 3. Evaluation and management of hypoglycemic events

Potential cause	Factors	Management
Insulin action profile	What was the timing and duration of insulin administration? What is the peak insulin action?	Consider rapid-acting and long-acting insulin analogs for multiple daily injections for more physiological insulin delivery Consider insulin pump therapy (89) Consider dual-wave insulin bolus with low glycemic meals (90) Consider sensor-augmented pump therapy with automated insulin suspension, which has been shown to duration and severity of severe hypoglycemia (80)
Recent food intake	What was the timing and amount of carbohydrates? What was the peak glucose effect of recent food intake?	Review determination of carbohydrates Review fat and protein content of meals (91) Adjust food intake so that glycemic peaks are more closely matched to insulin action peaks Daytime and bedtime snacks may need to be added, especially in younger children, or if intermediate-acting insulin is used
Recent physical activity	What was the timing, duration, and intensity of recent activity?	Pre-exercise and postexercise snacks (15–30 g) may be required Suspension of pump basal rate during exercise (30) If exercise occurs at peak insulin action, additional carbohydrates may be required
Recent hypoglycemia	Has there been recent recurrent, severe hypoglycemia? This may be associated with reduced counterregulatory response	Glucose targets may need to be adjusted upward in patients with recurrent hypoglycemia and/or hypoglycemia unawareness (75, 76)
Lack of hypoglycemic symptoms or hypoglycemia unawareness	At what glucose level do you start to recognize hypoglycemia? What types of symptoms do you have?	Consider increased monitoring of blood glucose levels Consider the use of real-time continuous glucose monitoring together with adjustment of glucose targets to avoid hypoglycemia and potentially reverse hypoglycemia unawareness (75, 76)
Prolonged, nocturnal hypoglycemia	What are the glucose values overnight? Blood glucose monitoring, in particular overnight, is important in detecting hypoglycemia and preventing serious and severe episodes	Consider increased overnight monitoring of blood glucose levels Consider retrospective continuous glucose monitoring to evaluate for patterns of asymptomatic nocturnal hypoglycemia Consider real-time continuous glucose monitoring

reduction 3 (STAR3) (77), have failed to show a reduction in hypoglycemia. Despite the use of CGM, there was still a high incidence of prolonged nocturnal hypoglycemia. There is evidence that patients sleep through 71% of alarms (78) and that adolescents with type 1 diabetes have a high acoustic arousal threshold from sleep (79). During the overnight period, the presence of CGM alone is unlikely to prevent severe nocturnal hypoglycemia.

Sensor-augmented pump therapy with low glucose insulin suspension

The advent of sensor-augmented pump therapy with low glucose insulin suspension allowing insulin to be

automatically suspended for up to 2 h when sensor glucose falls below a preset threshold, has the potential to reduce the duration of hypoglycemia, in particular at night, and is a significant development toward full automation of insulin delivery in patients with type 1 diabetes.

A recent randomized controlled trial (80) has been the first to show a reduction in severe hypoglycemia, defined as hypoglycemic coma or convulsion, with the use of sensor-augmented pump therapy with low glucose insulin suspension. This study recruited 95 patients, aged between 4 to 50 yr, all with impaired awareness of hypoglycemia. Subjects were randomized to either insulin pump therapy only or sensor-augmented pump with automated insulin suspension

at a preset threshold of 3.3 mmol/L (60 mg/dL). At the end of the 6-month study, there were six severe hypoglycemia events in the pump-only group and no events in the automated insulin suspension group. There was also less sensor-detected time spend <3.9 mmol/L (70 mg/dL) during the day and night periods. This was achieved with no deterioration in A1C. This trial selectively recruited high risk patients with impaired awareness of hypoglycemia and demonstrated a significant reduction in severe hypoglycemia.

Sensor-augmented pump therapy at this stage may be difficult to sustain indefinitely, particularly in children and adolescents. This in part is related to calibration alarms, sensor signal alarms, accuracy, and skin irritation secondary to sensors and adhesives. Despite this qualification these systems offer potential for improved glycemic control without increased hypoglycemia.

Predictive low glucose insulin suspend algorithms based on continuous glucose measurements have been developed and tested in a number of clinical trials (81, 82). These algorithms are designed to suspend insulin delivery prior to hypoglycemia occurring and in contrast to fixed suspend algorithms, also have the ability to resume insulin delivery based upon the rate of change of sensor values. In a home study of 45 participants using a predictive low glucose suspend system over 6 wk, there were fewer nights with at least one sensor value ≤ 60 mg/dL on intervention nights (21%) compared to control nights (33%), $p < 0.001$ (82).

Closed-loop insulin delivery systems

Automated insulin delivery, with continuous glucose sensing and insulin delivery without patient intervention, offers the potential to circumvent the significant glycemic excursions associated with conventional therapy. Early reports from clinical studies evaluating closed-loop prototypes suggest improved glucose control and a reduced risk of hypoglycemia (83–86). In general, these systems utilize input from a CGM system, an insulin pump for insulin delivery and a control algorithm, which can be located on a bedside computer, a smartphone or potentially, be integrated into the insulin pump and sensor system. A recent study of overnight closed-loop control in children with type 1 diabetes over multiple nights at diabetes camp, demonstrated an increased percent time spent in range (70–150 mg/dL) during the overnight period for closed-loop nights (73%) compared to sensor-augmented pump nights (52%), as well as reduction in time spent in the hypoglycemic range (87). The move to outpatient, ambulatory studies testing both day and night glucose control requires a robust system demonstrating not only efficacy but also with appropriate safety modules such as limitations on maximum insulin

delivered, fault detection algorithms for individual system components and flawless communication between devices (88). Perhaps most important is development of the user–device interface, given that with current available sensors and insulin, there will be some degree of patient input required for closed-loop operation (Table 3).

Conflicts of interest

The authors have declared no conflicts of interest.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Sick day management in children and adolescents with diabetes

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1–3).

Executive summary and Recommendations

- The diabetes care team should provide clear guidance to patients and families on how to manage diabetes during intercurrent illnesses as well as how they or other emergency medical personnel can be reached (diabetes team telephone contacts, mobile telephones, emergency medical assistance procedures) and such education should be repeated periodically to avoid the complications of:
 - ketoacidosis
 - dehydration
 - uncontrolled or symptomatic hyperglycemia
 - hypoglycemia
- Never completely stop insulin (A)
- When vomiting occurs in a child or adolescent with diabetes, it should always be considered a sign of insulin deficiency until proven otherwise (E)
- The insulin dose usually needs to be increased when there is fever or with most general or respiratory illnesses based on knowledge of symptoms and

signs especially knowledge of ongoing monitored blood glucose (BG) and/or urine or blood ketone levels (E):

- 1 Elevated BG with an absence or only small amount of ketones:
 - Give 5–10% of the total daily dose (TDD) of insulin (~0.05–0.1 U/kg) as short or rapid-acting insulin subcutaneously or intramuscularly and repeat this same dose every 2–4 h according to BG response and clinical condition. TDD of insulin is the sum of all long, intermediate and short/rapid-acting insulins usually taken.
- 2 Elevated BG with moderate or large amount of ketones is more serious and reflects actual or impending diabetic ketoacidosis (DKA) with potential for coma or death:
 - Give 10–20% of the TDD of insulin (~0.1–0.2 U/kg) as short or rapid-acting insulin subcutaneously or intramuscularly and repeat this same dose every 2–4 h according to BG response and clinical condition.

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- Insulin doses may need to be increased considerably in children who are in the partial remission phase, often up to 1 U/kg (E).
- Blood ketones are preferred over urine ketones when available and affordable, and the use during illness can reduce emergency room visits and hospitalizations (B).
- Strive for a BG between 4 and 10 mmol/L (70–180 mg/dL) and blood ketones below 0.6 mmol/L when the child is ill (E).
- The insulin dose often needs to be decreased when there is gastroenteritis, but should not be lowered to the extent that ketones are produced (E).
- In a child or adolescent with an intercurrent illness, URGENT specialist advice must be obtained when (E):
 - the underlying condition is unclear, fever persists, or family members are uncomfortable providing home care for any reason
 - weight loss continues suggesting worsening dehydration and potential circulatory compromise
 - vomiting persists beyond 2 h (particularly in young children)
 - parents are unable to keep BG above 3.5 mmol/L (60 mg/dL)
 - BG continues to rise despite extra insulin
 - fruity breath odor (acetone) persists or worsens
 - ketonuria is heavy and increasing/persistent or blood ketones are >1–1.5 mmol/L
 - the child or adolescent is becoming exhausted, confused, hyperventilating (? Kussmaul breathing) or has severe abdominal pain
 - change in neurologic status, mental confusion, loss of consciousness, seizures, progression of confusion may indicate impending or present cerebral edema; and treatment of cerebral edema is a medical emergency requiring immediate assistance with advanced medical facilities to prevent morbidity and mortality
 - the child is very young (<2–5 yr)
 - diabetes is not the only diagnosis, e.g., concomitant Down Syndrome or other mental illness, epilepsy, malaria, parasitic infections etc.
 - patients/relatives are exhausted or do not have the facilities or capability of providing needed care, e.g., intellectual, emotional and/or financial constraints, unavailability of insulin or any monitoring possibilities
 - caretaker understanding/language problems make it difficult to communicate with the family
 - if at any time the patient and/or adult caretakers request, emergency medical consultation should be facilitated including appropriate transport as possible according to the circumstances, ways to contact medical personnel and systems in place

for initial sugar and electrolyte solutions to be started while awaiting emergency treatment and evacuation to higher level facilities.

Five General Sick Day Diabetes Management Principles:

- More frequent BG and ketone (urine or blood) monitoring
- **DO NOT STOP INSULIN**
- Monitor and maintain salt and water balance
- Treat the underlying precipitating illness
- Sick day guidelines including insulin adjustment should be taught soon after diagnosis and reviewed at least annually with patients and family members with a goal of minimizing and/or avoiding DKA and similarly minimizing and/or avoiding illness associated hypoglycemia.

The effects of illness on diabetes

Children and teenagers whose diabetes is under good metabolic control should not experience more illness or infections than children without diabetes. While there are very few well done controlled prospective studies about intercurrent illness in type 1 diabetes, one study of adult patients with type 1 diabetes reported a higher risk of urinary tract, bacterial skin, or mucous-membrane infections but upper respiratory-tract infections were no more frequent than in controls (1) There is some evidence of impaired leukocyte function in poorly controlled diabetes (2) and children with poor metabolic control may have altered immune function, increasing susceptibility to and delayed recovery from infection. One pediatric study found low IgG concentrations and reduction in complement protein 4, variant B (C4B) levels related to impaired metabolic control (3) and it is tempting to believe – but not scientifically validated – that chronic hyperglycemia might be associated with more problems. (4, 5). In many parts of the world pediatric and adolescent diabetes care is woefully inadequate because of a general lack of resources, lack of health care systems, and availability of care as well as the enormous costs of insulin. This all contributes to produce a state of chronic underinsulinization because insulin is simply too expensive or unavailable. As a result, chronic poor diabetes metabolic control exists. Prevention of DKA not only requires more insulin availability but also awareness of the increased risk of DKA, coma, and death associated with normal infections precipitating decompensation (5).

Some illnesses, especially those associated with fever, raise BG levels because of higher levels of stress hormones promoting gluconeogenesis and insulin

resistance (6). Illness often increases ketone body production due to inadequate insulin levels. In contrast, illness associated with vomiting and diarrhea (e.g., viral gastroenteritis) may lower BG with the increased possibility of hypoglycemia rather than hyperglycemia. Decreased food intake, poorer absorption, and a slower emptying of the stomach or overt diarrhea with more rapid transit during gastroenteritis may contribute to such hypoglycemia. Sometimes there are increased insulin requirements during the incubation period of an infection for a few days before the onset of the illness. The increased need for insulin may persist for a few days after the illness has passed presumably due to insulin resistance but all such descriptions are highly variable from one person to another and even from one illness to another. In the midst of a typical viral self-limited 'epidemic,' however, patterns may occur which facilitate making some generalizations from which advice for subsequent patients may be based.

More frequent monitoring

Glucose

- Frequent BG monitoring facilitates optimal management during illness (with adult supervision especially in adolescents)
- BG should be monitored at least every 3–4 h including through the night and sometimes every 1–2 h

Sick day preparation

- Urine glucose can still be utilized if BG testing equipment is not available (6).
- If routine BG testing is not available for any reason, then some emergency supplies should ideally be provided to be 'saved' for episodes of illness instead of for day-to-day monitoring according to appropriate individual local circumstances (7).
- Distinguishing those illnesses associated with hyperglycemia from those associated with hypoglycemia is facilitated by BG monitoring (5, 6, 8, 9).
- Insulin adjustments (sick day extra doses) and other insulin changes take place in direct relationship to the ongoing BG monitoring results (see below).

Ketones

Ketones are produced by the liver from free fatty acids that are mobilized as an alternative energy source when there is a lack of glucose for intracellular metabolism. Starvation ketones are produced when the BG is low. Ketones are also produced when insulin is lacking to initiate the transport of glucose from the blood

stream into the cell. Ketones accumulate because of increased lipolysis, increased ketogenesis and decreased ketone body utilization due to low insulin levels. Urine strips measure acetoacetate (AcAc) and acetone itself while blood strips measure beta-hydroxybutyrate (BOHB). In acute ketoacidosis, the ketone body ratio (BOHB:AcAc) rises from normal (1:1) to 10:1 or more (10). In response to insulin therapy, BOHB levels commonly decrease long before AcAc levels do. The frequently employed nitroprusside test only detects AcAc in blood and urine and so routine urine ketone monitoring often shows prolonged ketonuria even when significant ketoacidosis and ketonemia have already responded to treatment (10). This results in some confusion at home because there seems to be more prolonged ketonuria compared to clinical improvement when sick day management has been successful; in hospital settings and emergency rooms, this may also produce the incorrect response of wanting more and more insulin to be given to 'clear' the ketones from the urine rather than understanding the physiology of what is metabolically taking place and what is actually being measured. Blood ketone testing helps to allow better understanding and therefore when to start to back down on aggressive extra insulin provision (5, 6, 9, 10).

Urinary ketone tests (liquid or test strips for acetone and AcAc levels) or, when available, blood ketone tests (for BOHB), help to guide sick day management. Blood ketone testing (measuring BOHB) provides additional information to urine ketone testing:

- Blood BOHB >0.5 mmol/L is abnormal in children with diabetes (11, 12).
- Adult studies have shown that the time delay after a pump stop to diagnosis of ketosis is significantly longer for ketonuria than for plasma ketonemia (13) and that a urinary ketone test can remain positive more than 24 h after resolution of an episode of ketoacidosis in over half of patients studied (14).
- There may be dissociation between urine ketone (AcAc) and blood BOHB concentrations which may be increased to levels consistent with DKA when a urine ketone test is negative or shows only trace or small ketonuria (5, 15).

Home measurement of blood BOHB concentrations in children and adolescents enables earlier identification and treatment of ketosis, when compared to urine ketone testing, and decreases diabetes-related hospital visits (both emergency department visits and hospitalizations) (16–18).

Blood BOHB measurements may be especially valuable to prevent DKA in patients who use an insulin pump as only rapid- or short-acting insulin is used in this type of therapy. Elevations in blood

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BOHB may precede elevations in urine ketones due to interrupted insulin delivery (14) (e.g., catheter occlusion or dislodgement), which can rapidly lead to ketogenesis and ketosis as well as increased insulin needs associated with intercurrent infections.

- During resolution of ketosis, blood BOHB normalizes sooner than urine ketones (5). Monitoring BOHB may also have the potential to help prevent late hypoglycemia from overtreatment with insulin based upon the persistence of ketonuria at the same time the ketonemia is improving.
- Blood BOHB monitoring may be especially useful in very young children or when urine specimens are difficult to obtain.

Households should maintain readily available supplies and information for sick day management including:

- Written information on management and important contact numbers/addresses of health care team
- Telephone availability has been shown in several clinical studies to facilitate communication, allow for earlier advice and institution of sick day guidelines and decrease or minimize clinical decompensation and avoid emergency room use as well as decrease hospitalization rates (19–21).
- Sick day foods and hydration supplies such as chicken soup, broths.
- Sufficient glucose and ketone monitoring supplies, additional insulin and an emergency glucagon kit.

Never stop insulin

The insulin dose may need to be increased or decreased to maintain glucose metabolism.

- The most common mistake made by health care providers and caregivers who are unfamiliar with diabetes is to advise the complete omission of insulin because ‘the child is ill and not eating,’ thus increasing the risk of frank DKA. (5, 6, 8)
- Even in the fasting state, some insulin is still required for basal metabolic needs, which may go up during an acute illness situation so that more frequent monitoring of BG and ketones is required.
- Insulin doses may go up during an acute illness situation so that more frequent monitoring of BG and ketones is required.
- If episodes of hyperglycemia, ketosis, and vomiting recur, with or without infection, it should be recognized that this may be due to omission (22) or inadequate administration of insulin. Insulin omission is particularly problematic during adolescence (23) and almost always represents a

severe psychosocial issue, ie. sexual or physical trauma, emotional trauma or abuse, poorly treated or unrecognized anxiety or depression, learning problems, executive dysfunction and/or attention deficit disorders or some combination. Family dysfunction frequently occurs under such circumstances and may contribute to the recurrence DKA episodes either directly or indirectly. (24) Lack of appropriate adult supervision needs to be considered with appropriate therapeutic interventions put into place since recurrent DKA has a high association with DKA-related complications including coma and death. (5, 6, 9, 10)

Loss of appetite

Replacing meals with easily digestible food and sugar-containing fluids provides energy (carbohydrates) and may help prevent further ketosis. Necessary sick day management supplies at home include the following:

- glucose tablets, sweets, or candies such as jelly beans or Lifesavers® as well as dried fruit to prevent hypoglycemia
- Clean (boiled/purified), cool water to provide hydration and prepare salty soups
- sugar and electrolyte containing fluids such as sports drinks, electrolyte mixtures, Pedialyte®, Kool-Aid® or even sugar-containing ginger-ale or colas to provide hydration, glucose, and salts
- easy to digest carbohydrates such as crackers or rice

Maintaining hydration with salt and water

- Hyperglycemia, fever, excessive glycosuria, and ketonuria all contribute to increased fluid losses.
- Sick day cabinets should contain supplies as above to prevent dehydration.
- Liquids for hydration should contain salt and water and not just plain water especially if there are ongoing losses associated with vomiting or diarrhea. Chicken soup or clear broths are an excellent source of not only water but also sodium salt and some potassium, all needed for assistance with maintenance of hydration as well as avoiding mineral and water imbalance in conditions leading up to DKA (5, 6, 8–10). If appetite is decreased or the BG is falling below 10 mmol/L (180 mg/dL), sugar-containing fluids should be considered to decrease starvation ketosis (e.g., sports/electrolyte drinks, pediatric electrolyte mixtures, diluted fruit drinks, colas, ginger ale, etc.) (5, 6, 8–10). It may be reasonable to remove excessive carbonation (bubbles) in some soft drinks to minimize any potential indigestion. This can be achieved by

opening the containers and allow time for bubbles to escape with a little bit of shaking/stirring as well (25).

- Elevated levels of ketones, whether associated with low BG (starvation) or high BG (insulin deficiency), contribute to nausea and vomiting and may lead to decreased food and fluid intake, further elevated levels of ketones and worse dehydration as well as (decompensated) ketoacidosis (5, 6, 9, 10).
- Especially in young children with diabetes, intravenous fluids may be required if nausea, vomiting or diarrhea are persistent and associated with ongoing weight loss in order to prevent cardiovascular collapse, hypotension, coma, and death (5, 6, 9, 10).

Specific medical advice: treat the underlying precipitating illness

The underlying illness should be treated as it would be for a child or adolescent without diabetes (i.e., antibiotics for bacterial infections but not viral infections) 5, 6, 9, 10. In some parts of the world, specific endemic or epidemic illnesses have to be considered [e.g., dengue hemorrhagic fever (DHF), malaria, gastrointestinal parasitic infections etc.]. Monitoring and clinical manifestations of these may be complicated in diabetes patients (8). Treating fever, malaise and headache with antipyretics or pain medications such as paracetamol, acetaminophen, or ibuprofen is acceptable but not mandatory.

- Sick day home supplies can include enteral and rectal preparations for fever management.
- Unknown or uncertain alternative medicine co-prescription should be avoided and, as part of education efforts, acknowledged and reviewed in advance and periodically thereafter.
- Vomiting may be caused by either:
 - 1 the illness itself (i.e., gastroenteritis, unclean food or food poisoning, surgical condition or other illness)
 - 2 low BG
 - 3 lack of insulin resulting in high BG and ketosis.
- Unless food poisoning is suspected, consider treatment of vomiting with single injection or rectal administration of anti-emetics (e.g., Ondansetron, Promethazine suppositories) to help oral intake of carbohydrate unless concerns about mental status exist. However, in the case of high BG and an excess of ketones, priority should be given to administering extra insulin as well as sufficient salt and water solutions. In this situation, the vomiting often stops once extra insulin has been given to reverse ketosis.

- Oral medicines for symptomatic relief of vomiting or diarrhea have no proven efficacy and are therefore not usually recommended. However, if available, loperamide or similar anti-diarrheal medication, bismuth subsalicylate® combinations may be used to help provide symptomatic relief (6).

Additional insulin

- Additional doses of short/rapid-acting insulin are required with careful monitoring to reduce BG, prevent ketoacidosis, and avoid hospital admission (5, 6, 8–10).
- Both rapid-acting insulin analogs as well as older, more traditional short acting insulin (synthetic or animal-origin) can be used to provide supplemental insulin during sick days depending upon availability and cost.
- The dose and frequency of injection will depend on the level and duration of hyperglycemia as well as the severity of ketosis. Such supplemental doses are usually given subcutaneously but may also be given intramuscularly with healthcare professional advice.
- If there is hyperglycemia with negative or small amounts of ketones, usual recommendations are to give an additional 5–10% of TDD of bolus and basal insulins added together to provide calculations for this supplemental (booster) dose (approximately 0.05–0.1 U/kg) as short/rapid acting insulin administered urgently and this supplemental sick day dose may be repeated every 2–4 h based upon BG monitoring results (see Table 1).
- If there is hyperglycemia and more marked ketonuria (moderate to high), usual recommendations are to give an additional 10–20% of TDD (approximately not more than 0.1 U/kg) as short-/rapid-acting insulin. This dose should be repeated every 2–4 h; based upon frequent glucose and ketone results (see Table 1), response to the supplemental dose, clinical status and hydration status.

The additional dose recommendation of 0.05–0.1 U/kg is a general recommendation for children and adolescents with standard insulin requirements of approximately 0.7–1 U/kg/day. However, for children or adolescents who have low usual daily insulin requirements or those with insulin resistance and high insulin requirements, the percentage (%) calculations may work more readily rather than the 0.1 U/kg empiric additional dose

- When patients in remission phase are ill (during ‘the honeymoon phase’) there may be a need to increase insulin up to 1 U/kg/day very quickly.

Table 1. How to calculate sick day booster fast acting insulin dosage (5, 7–10) [E]

How to calculate the Amount of Extra Insulin on Sick Days				[E]. No data are available from clinical trials		
Ketones		Blood glucose				
Blood ketones mmol/L	Urine ketones	<5.5 mmol/L <100 mg/dL	5.5–10 mmol/L 100–180 mg/dL	10–14 mmol/L 180–250 mg/dL	14–22 mmol/L 250–400 mg/dL	>22 mmol/L >400 mg/dL
<0.6	Negative or trace	Do not give extra insulin. May need to consider minidoses of glucagon (see Table 2) if <4 mmol (70 mg/dL) Check BG and ketones again in 2 h	No need to worry	Increase dose of insulin for next meal if BG is still elevated	Give extra 5% of TDD or 0.05 U/kg	Give extra 10% of TDD or 0.1 U/kg. Repeat if needed
0.6–0.9	Trace or small	Starvation ketones. Extra carbohydrates and fluid are needed	Starvation ketones. Extra carbohydrates and fluid are needed	Give extra 5% of TDD or 0.05 U/kg	Give extra 5–10% of TDD or 0.05–0.1 U/kg	Give extra 10% of TDD or 0.1 U/kg. Repeat if needed
1.0–1.4	Small or moderate	Starvation ketones. Extra carbohydrates and fluid are needed	Starvation ketones. Extra carbohydrates and fluid are needed. Give ordinary bolus dose	Extra carbohydrates and fluid are needed. Give 5–10% of TDD or 0.05–0.1 U/kg	Give extra 10% of TDD or 0.1 U/kg	Give extra 10% of TDD or 0.1 U/kg. Repeat if needed
1.5–2.9	Moderate or large	High levels of starvation ketones. Check BG meter. Recheck BG and ketones. Extra carbohydrates and fluid are needed	High levels of starvation ketones. Extra carbohydrates and fluid are needed. Give 5% of TDD or 0.05 U/kg. Repeat when BG has risen	Extra carbohydrates and fluid are needed. Give 10% of TDD or 0.1 U/kg	Give extra 10–20% of TDD or 0.1 U/kg. Repeat dose after 2 h if ketones do not decrease	
≥0	Check BG and ketones every hour Large	Very high levels of starvation ketones. Check BG meter. Recheck BG and ketones. Extra carbohydrates and fluid are needed	Very high levels of starvation ketones. Extra carbohydrates and fluid are needed. Give 5% of TDD or 0.05 U/kg. Repeat when BG has risen	Extra carbohydrates and fluid are needed. Give 10% of TDD or 0.1 U/kg	Give extra 10–20% of TDD or 0.1 U/kg. Repeat dose after 2 h if ketones do not decrease	
There is an immediate risk of ketoacidosis if the blood ketone level is ≥3.0 mmol/L Insulin treatment is needed urgently! Consider evaluation of patient at emergency department						

BG, blood glucose; TDD, total daily dose.

To calculate the total daily dose (TDD), add up all the insulin given on a usual day (i.e., rapid-/shortacting + intermediate/long-acting) or sum of basal rate and boluses in a pump. Do not include additional boluses given for unexpected hyperglycemia. High blood glucose and elevated ketones indicate a lack of insulin. ‘Starvation blood ketones’ are usually below 3.0 mmol/L. When the child is feeling sick or vomits, and the BG is below 10–14 mmol/L (180–250 mg/dL, see table), he/she must try to drink sugar-containing fluids in small portions to keep the BG up. When ketone levels are raised, priority is to give extra insulin, and this will be difficult if BG is low. Extra insulin may be given as rapidacting insulin analogues or short-acting regular insulin, but rapid-acting if available is preferred. Short-acting insulin can be given intramuscularly to speed up absorption. The ketone level may increase slightly (10–20%) within the first hour after giving extra insulin, but after that it should decrease [E].

- During illness it also may be necessary to increase basal insulin doses whether by multiple injection therapy or when using an insulin pump. With a pump, temporary basal rate increases of 20% to as high as 50 or 100% may be used until the BG begins to normalize and the ketones clear based upon ongoing BG, ketone monitoring and clinical response.

Example: A sick child has BG 14–20 mmol/L (i.e., 250–360 mg/dL) with moderate urinary ketones and/or blood ketones of approximately 1.5 mmol/L. Advise 10–20% of total daily insulin dose (or 0.1 U/kg) as short/rapid acting insulin every 2–4 h until BG falls to <14 mmol/L (<250 mg/dL). Thereafter any additional doses might be 5–20% of TDD. Check urine ketones at every voiding. If available, check blood ketones and recheck hourly if elevated (>0.6 mmol/L).

- After extra insulin has been given, the blood ketone level may temporarily increase by 10–20% for the first hour or two but should be expected to decrease thereafter.
- Urine ketones often stay elevated for many hours because of the body’s conversion of blood BOHB into AcAc which then can be measured with urine testing (5). Acetone can be stored in fat tissue during ketosis and, along with conversion of BOHB to AcAc, may contribute to persistent urine ketones despite interruption of total ketogenesis with insulin and fluid administration (5).

When ketone testing is not available

It is strongly recommended that some form of ketone testing be available, and urine strips are a relatively cheap investment. However, in some circumstances, no ketone testing may be available or affordable. In these situations it must be emphasized that during intercurrent infections, BG testing remains very important in helping to avoid worsening ketoacidosis

and to prevent hospital admission as well as progression of DKA to coma and death (5, 6, 8). It is helpful to provide written advice on how much additional insulin to give for particular levels of BG (as in Table 1) or when body weight is not available to advise on particular extra doses of insulin according to the child or adolescent’s age and usual TDD (8, 9). Periodic review and re-teaching should also be considered at least on an annual basis and actually documented in the medical records by staff.

Infections associated with hypoglycemia

- These infections are usually viral gastroenteritis diagnoses and are often associated with nausea and vomiting with or without diarrhea. Any illnesses associated with more gastrointestinal symptoms rather than respiratory symptoms would fall into this category. Advise replacing meals with frequent small volumes of sugary drinks that also contain sodium (salts) and maintain careful BG monitoring with consideration for temporary reduction (but not elimination) of insulin dosage (5, 6, 8–10).
- Do not give non-sugar fluids in this situation.
- Give sufficient fluids to maintain hydration. Keep records of how much the child has had to drink.
- Attention to urinary output and measurement of body weight at home every 4–6 h can serve as a guide to fluid needs. Steady weight suggests adequate hydration and fluid replacement whereas ongoing weight loss would usually require telephone or other contact with health care personnel to assess need for emergency room or hospital intravenous fluid treatment (5, 6, 8–10).
- Reduction of total daily insulin dose by 20–50% may be required if there is concomitant hypoglycemia and not hyperglycemia as indicated above (5, 6, 8–10) but if the doses are lowered too much, there is a risk of developing insulin deficiency leading to ketosis and ketoacidosis.

Table 2. Recommended dose for mini-dose glucagon [B]*

Age (yr)	Quantity			
	Ugm	mg	cc’s (1 mg/cc)	Units on insulin syringe
<2	20	0.02	0.02	2
2–15	10 per yr of age	0.01 per yr of age	0.01 per yr of age	1 per yr of age
>15	150	0.15	0.15	15

Note that the doses recommended above are quite different (lower) from emergency doses given in case of severe hypoglycemia.

*Correction boluses to correct hyperglycemia can be given at any time or added to meal boluses. A useful guide to estimate correction doses is to employ the ‘100’ rule (the TDD is divided into 100 to estimate the number of mmol/L that the BG will fall by giving 1 U of insulin) (24, 25) (C, C, and E). For mg/dL, use the ‘1800 rule’, i.e., divide 1800 by the TDD. For example, for a patient on 50 U of insulin per day, the PG should fall by approximately 2 mmol/L (36 mg/dL) for each additional 1 U of insulin. During illness, the correction factor can be recalculated every day to match the increasing (or decreasing) insulin requirements. This calculation can also be used to estimate a negative correction to correct for hypoglycemia [in a patient on 50 U of insulin a day, giving 1 U less at meal times should allow the PG to rise by 2 mmol/L (36 mg/dL)].

- Check ketones regularly as a guide to determine that the child or adolescent has sufficient carbohydrate/sugar intake. Ketones associated with gastrointestinal illnesses and hypoglycaemia usually reflect inadequate energy supply rather than insulin deficiency (i.e., starvation ketones) but both reasons may occur in any individual situation.
- If hypoglycemia (<3.5–4 mmol/L, 65–70 mg/dL) and nausea or food refusal persists, a modified, smaller-than-usual glucagon injection – if available – may reverse the hypoglycemia and enable oral fluid intake to be re-established ('mini glucagon treatment') (26, 27) (see Table 2). Repeat after 1 h or more if needed. If hypoglycemia persists and glucagon is not available, emergency services will be required but simple sugar in the buccal cavity or honey or molasses may also be provided as long as there is a determination that there is no significant neurologic compromise where aspiration may occur.

Specific advice regarding sick day management on insulin pumps

The key points of sick day management, mentioned previously, are the same for pump users as for those

on insulin injections (9, 28, 29). Patients on pumps use only rapid- or short-acting insulin and do not have any injected depot of long-acting insulin. With pumps DKA can develop rapidly with either interruption of insulin delivery or intercurrent illness to which there is no increased insulin response. Episodes of hyperglycemia must be taken very seriously especially if associated with positive urine and/or blood ketones. If the BG level is 14 mmol/L (250 mg/dL) or above in an insulin pump patient, the following steps should be taken:

- Immediately check for problems with the pump or delivery system and change the infusion set, tubing and reservoir of insulin. Kinks in the catheter, air in the infusion line, disconnected catheters especially at the insertion site or insertion site irritation all get identified when patient and family members are instructed to first change the infusion set and second, give an immediate injection by syringe or pen to be certain that insulin is being delivered.
- Check for ketones in the blood or urine.
- Proceed as directed in Table 3 depending on ketone result. In case of ketosis, extra insulin should always be given with a pen or syringe, not with

Table 3. Management of sick days and hyperglycemia with insulin pump (8) [E]

Ketones negative	Blood ketones >0.6 mmol/L or positive urine ketones or apparent that pump is not working or catheter blocked, dislodged etc.
<p>Give correction bolus with pump Test BG hourly to confirm that BGs move downward</p> <p>Drink low-carbohydrate fluids or salty liquids (i.e., soup) If BG lower after 1 h, recheck again in 1–2 more hours to decide if another bolus is needed If BG not lower on recheck, then give bolus by syringe or pen and follow instructions in second column</p>	<p>May be a pump delivery or site problem or an illness Give sick day bolus by injection with pen or syringe using Table 1 guidelines for sick day booster 5–10–20% rule Change the catheter and check to be sure pump is working Continue to follow sick day booster guidelines using pen or syringe until BGs respond Re-establish insulin pump infusion with new set and cannula with temporary basal rate increase of approximately 120–150% depending upon BG and ketone results Monitor BG hourly and recheck ketones and weight at least every 4 h Drink extra high-carbohydrate fluids if the ketones are elevated and BG is low and extra low-carbohydrate 'diet' fluids if BG is elevated with or without elevated ketones If after 2 h there is no improvement, liaise with diabetes pump team If after 2 h the BG is improved, use the unused bolus rule to decide if an additional bolus is needed.* Pump use can be resumed BG remains high, ketones persist, or nausea, vomiting, or abdominal pain develop, confusion or problems staying awake and alert, contact the diabetes pump team or proceed to immediate hospital assessment</p>

BG, blood glucose; TDD, total daily dose.

*Correction doses given for hyperglycemia should take into consideration the residual effect of any previous meal or correction bolus dose. A useful guide is to use the 'unused bolus rule' (approximately 30% of a rapid-acting insulin bolus is absorbed each hour). The correction dose should be reduced accordingly. For example, if 5U had been given as a meal bolus 2 h previously, 60% would have been absorbed and the remaining 40% or 2U would still be exerting an effect. This should be subtracted from any correction dose. However, most pumps have this 'insulin on board' included in the 'bolus guide', and you need then not subtract it manually if this function is activated.

the pump (as malfunction may be the cause of ketosis).

- To overcome insulin resistance, the basal rate may be increased from 120% to 150% according to BG and ketone results and, at the same time, correction boluses also may need to be increased by 10–20% during the period of illness.
- Meal insulin boluses may need to be decreased when the hyperglycemia has been corrected because patients may be eating less and their gastrointestinal absorption may be poor during the illness. Hypoglycemia should be treated in the usual way. The basal insulin rate may also need to be decreased if the BG still tends to be low provided the ketones continue to be negative.

Conflicts of interest

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Exercise in children and adolescents with diabetes

Robertson K, Riddell MC, Guinhouya BC, Adolfsson P, Hanas R. Exercise in children and adolescents with diabetes. *Pediatric Diabetes* 2014; 15 (Suppl. 20): 203–223.

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- Tailor insulin regimen to activity (B). Multiple daily injections or a pump may be easier to combine with active exercise.
- Discuss the percentage reductions in insulin before exercise (C).
 - When exercise is planned at a time of peak insulin action, a marked reduction in dose should be made.
 - The pump needs to be disconnected or a temporary basal rate implemented at least 90 min before starting the exercise to give a reduced basal effect.
 - Do not inject the insulin in a site that will be heavily involved in muscular activity.
- Discuss type and amount of carbohydrate (CHO) required for specific activities (B).
- Any exercise is dangerous and should be avoided if pre-exercise blood glucose levels are high (>14 mmol/L, 250 mg/dL) with ketonuria (small or more)/ketonemia (>0.5 mmol/L). Give approximately 0.05 U/kg or 5% of total daily dose (TDD, including all meal bolus doses and basal insulin/basal rate

in pump) and postpone exercise until ketones have cleared (B).

- Consume up to 1.0–1.5 g of CHO per kilogram of body mass per hour of strenuous or longer duration exercise when circulating insulin levels are high, if pre-exercise insulin doses are not decreased (B).
- Meals with high content of CHOs should be consumed shortly after the exercise event, taking advantage of the period of heightened insulin sensitivity to help replenish glycogen content and limit post-exercise hypoglycemia.
- Alcohol inhibits gluconeogenesis so hypoglycemia is more likely if consumed (A).
- Dehydration is a risk unless sugar-free fluids also are consumed (E).
- Use of detailed records of physical activity, insulin, food, and glucose results is important for good diabetes control during spontaneous physical activity and/or exercise. New technologies, e.g., embedded into Smartphones may be of use (E).
- Hypoglycemia may not only be anticipated during or shortly after exercise, but is also possible up to 24 h afterwards, due to increased insulin sensitivity (A).

- Measure blood glucose before going to bed and decrease bedtime basal insulin (or pump basal) by 10–20% after an afternoon or evening exercise session if the exercise was more intense than usual or an activity not performed regularly.
 - Short sprints added to aerobic training can minimize the risk of hypoglycemia
 - Extra CHO after the activity is often the best option to prevent post-exercise hypoglycemia when short duration and high-intensity anaerobic activities are performed.
 - A mixture between aerobic and anaerobic exercise (soccer, cycling, jogging, and swimming) will typically require extra CHO before, possibly during, and often after the activity.
 - The rise in blood glucose after intense exercise may be prevented by giving a small additional dose of rapid-acting insulin at half-time or immediately after the exercise is finished – for example, a 50% correction bolus when levels are >15 mmol/L.
- Risk of post-exercise nocturnal hypoglycemia is high, and particular care should be taken if bedtime blood glucose level is <7.0 mmol/L (125 mg/dL) with NPH basal insulin. With basal analogs, the bedtime glucose level can be slightly lower without a substantial risk of night-time hypoglycemia but no specific value is a guarantee that hypoglycemia will be avoided (E).
 - Patients who have proliferative retinopathy or nephropathy should avoid resistance-based exercises or anaerobic exercise that is more likely to result in high arterial blood pressure (E).
 - Care should be taken that the blood glucose meter and test strips chosen are suitable for the environment where they will be used (C).
 - High glycemic index snacks and hypoglycemia remedies should always be readily available at school (E).
 - Careful advice on and planning of travel, exercise, and management is essential (E).
 - A diabetes care plan containing written advice about exercise and sports should be provided for carers/teachers (E).
 - Professionals should take opportunity to attend camps for children with diabetes (E).
 - Continuous glucose monitoring (CGM) may have a role in helping to avoid hypoglycemia during and after exercise (C).
 - New pump technologies such as low-glucose suspend and programmed low glucose management may also be useful in the future (E).

Introduction

It is clear that it is important to encourage children and adolescents to be physically active, to be less

sedentary, to control their weight, and to develop healthy lifestyle habits that will be maintained. In children who already have diabetes, this will help to mitigate increased cardiovascular risk and in those who are not diabetic, physical activity will have an important role in prevention.

While this article is intended to address the issue of blood glucose regulation during various forms of sports and exercise, it is important for diabetes care professionals and parents to appreciate that the demands of day-to-day physical activity will also have to be considered if a young person is going to participate in any activity, which for them is unusually strenuous or prolonged.

In the 1950s, Joslin proposed that exercise is the third essential component in blood glucose regulation for persons with type 1 diabetes (T1D), after insulin and dietary management. Although most studies have shown little impact upon hemoglobin A1c (HbA1c) levels (1–3), and many only a brief improvement (4) unless the exercise was sustained for 6 months (5), a cross-sectional analysis of data on a larger group showed that the frequency of regular physical activity was associated with lower HbA1c without increasing the risk of severe hypoglycemia (6). Younk et al. have provided a useful review (7). The benefits of exercise go far wider and include weight control, reduced cardiovascular risk (8), and an improved sense of well-being (9).

There is growing evidence that the antecedents of cardiovascular risk begin early in diabetes (10) and studies have shown that exercise has a beneficial effects on various markers of vascular health including skin microvascular reactivity (11) and endothelial function (12). A systematic review of adult studies concluded that physical activity is associated with a marked decrease in cardiovascular and all-cause mortality in both men and women, even after adjusting for other relevant risk factors (8). Even if glucose targets, as measured by HbA1c are not achieved, regular physical activity is associated with reduced early mortality in the adult population (13).

For people with diabetes, post-meal low to moderate-intensity exercise can be a valuable way to minimize postprandial glycaemic spikes (14). For some, participation in physical activity is somewhat sporadic and related to leisure, school, or work. For others, daily exercise is part of an overall training or conditioning program.

Children and adolescents with diabetes should derive many of the same health and leisure benefits as adults and should be allowed to participate with equal opportunities and with equal safety.

Diabetes should not limit the ability to excel in a chosen sport. Many famous athletes have proved this, e.g., Sir Steve Redgrave – five times Olympic gold

medal winning rower, Kris Freeman – Olympic cross-country skier (four winter Olympics), Gary Hall – five time Olympic Gold Medal swimmer, Zippora Karz – ballerina, Wasim Akram – Pakistani cricketer at international level, Brandon Morrow – Major League baseball player, Cliff Scherb – Ironman Triathlete, Scott Verplank – PGA Tour golfer, and female professional golfer Mimmi Hjorth and Emil Molin – NHL ice-hockey player. There is now even a professional cycling team (Team NovoNordisk), with all the riders having T1D, which holds the record for the Race Across America and has aspirations for a Tour de France ride in 2021.

The topic most commonly discussed with families with regard to exercise is avoidance of hypoglycemia, but prevention of acute hyperglycemia/ketoacidosis may become a concern as well (15).

The HELENA study has demonstrated, in a large multi-center cohort of European adolescents without diabetes, that muscular fitness and cardiorespiratory fitness are independently associated with metabolic risk of insulin resistance (16) and therefore of type 2 diabetes (T2D). Part of this study showed that self-reported physical activity correlates negatively with insulin resistance (after adjusting for confounders such as waist–hip ratio) but that higher cardiorespiratory fitness reduces the impact so insulin resistance was less in those with the higher fitness (17). These findings have been supported by a recent Dutch study (TRAILS) which also showed that increased childhood fatness is associated with increased cardiometabolic risk but that this is, to some extent, mitigated by fitness (18).

The relationship between physical activity, sedentary behavior, fitness, and glycemic control is complex, as

suggested above, but several studies have found that children and adolescents with T1D are less fit than their non-diabetic peers, particularly if they are in poor glycemic control (19, 20).

Huge efforts are being made around the world to get children and adolescents to engage more in physical activity and to reduce sedentary behavior. A recent systematic review by MacMillan et al. has studied interventions aimed at youth with T1D (21).

Exercise physiology

Before considering the situation in T1D, it is useful to understand the ‘normal’ physiological responses to moderate-intensity aerobic exercise in the non-diabetic individual.

As shown in Fig. 1, non-diabetic individuals have a reduction in insulin secretion and an increase in glucose counterregulatory hormones facilitating an increase in liver glucose production that matches skeletal muscle glucose uptake during exercise. As a result of this precise autonomic and endocrine regulation, blood glucose levels remain stable under most exercise conditions (9).

Exercise has been shown to increase non-insulin dependent glucose uptake by muscle by the translocation of GLUT-4 receptors to the cell surface. Thus glucose uptake increases even when insulin levels are low (22).

Under conditions of intense exercise, catecholamines rise, tending to increase hepatic glucose production and limit glucose uptake into muscle, thereby promoting a brief and transient increase in glycemia, even in non-diabetic children. This increase is exaggerated

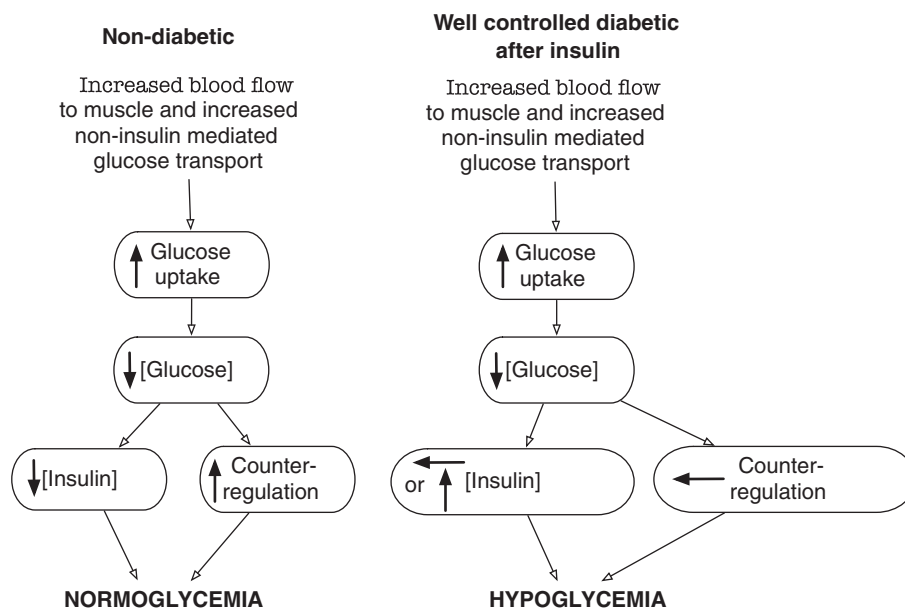


Fig. 1. Physiologic responses to exercise in the diabetic and non-diabetic individual (square brackets denote plasma concentration).

in children with T1D because of a failed increase in insulin secretion during the rise in glucose (23).

In T1D, the pancreas does not regulate insulin levels in response to exercise and there may be impaired glucose counterregulation, making normal fuel regulation nearly impossible. As a result, hypoglycemia or hyperglycemia commonly occurs during or soon after exercise.

Response to exercise

In real life, young people with diabetes have variable blood glucose responses to exercise. The blood glucose response to 60 min of intermittent exercise is reproducible in a child if the timing of exercise, the amount of insulin, and the pre-exercise meal remain consistent (24). Glucose production in healthy control subjects increases with exercise intensity and can be entirely attributed to increases in net hepatic glycogenolysis. In contrast, moderately controlled T1D subjects exhibit increased rate of glucose production both at rest and during exercise, which can be entirely accounted for by increased gluconeogenesis (25).

Young people with T1D have been found to have decreased aerobic capacity as measured by VO₂ max (percentage of maximal aerobic capacity), compared with non-diabetic control subjects (26) but this finding is contested by Adolfsson et al. in a detailed study of VO₂ max and endocrine response to different intensities of exercise (bicycle ergometer) in six reasonably well-controlled adolescents with diabetes and six non-diabetic controls of similar age. They found no significant differences except for higher growth hormone levels in those with diabetes (27). It is probably relevant that all participants in the latter study reported that they participated regularly in physical activity. Similarly, Cuenca García et al. compared 60 8–16 yr olds with diabetes with 37 sibling controls and found no difference in fitness or physical activity. They found that moderate to vigorous

physical activity was associated with better metabolic control and accounted for 30–37% of the variance in HbA1c (28).

Total-body insulin-mediated glucose metabolism in adolescents correlates with the degree of glycemic control as assessed by the level of glycosylated hemoglobin (29). However, even in the same individual, it is possible for the blood glucose to be increased, decreased, or unchanged by exercise dependent upon circumstances as indicated in Table 1.

Factors affecting glucose response to exercise

Intrinsic characteristics of the exercise

Duration and intensity. It is especially important to plan for long duration or intense aerobic exercise, or else hypoglycemia is almost inevitable. Nearly all forms of activity lasting >30 min will be likely to require some adjustment to food and/or a reduction in insulin.

Most team and field sports and also spontaneous play in children are characterized by repeated bouts of intensive activity interrupting longer periods of low to moderate-intensity activity or rest. This type of activity has been shown to produce a lesser fall in blood glucose levels compared with continuous moderate-intensity exercise, both during and after the physical activity in young adults (30). The repeated bouts of high-intensity exercise stimulated higher levels of noradrenaline that likely increased blood glucose levels. A study in adults (31) suggested that late hypoglycemia was more common after intermittent high-intensity exercise but the opposite was found by another conducted in trained athletes with T1D (32).

Moderate-intensity exercise (40% of VO₂ max) followed by an intense cycling sprint at maximal intensity prevented a further decline in blood glucose for at least 2 h after the exercise (33). However, typical team games may last up to 90 min and the results may not be

Table 1. Factors that affect changes in blood glucose during exercise

Hypoglycemia	Glucose unchanged	Hyperglycemia
Hyperinsulinemia due to proximity to or excessive dose of administered insulin (both bolus and basal). Exercise prolonged – usually more than 30–60 min and/or no extra carbohydrate intake. Moderate-intensity aerobic exercise (50–75% maximal aerobic capacity). Non-familiarity with an activity, requiring greater energy expenditure than when in a trained state.	Insulin pre-exercise adjusted appropriately. Appropriate carbohydrate consumed.	Hypoinsulinemic state prior to and during exercise. The emotion of competition eliciting an adrenal response. Short, intermittent bouts of intense anaerobic activity eliciting an increase in adrenal response. Excessive carbohydrate consumed Post-exercise, when glucose production exceeds utilization.

applicable to this length of physical activity. The same research group, from Perth, Australia, further studied this phenomenon and concluded that short duration sprinting increases blood glucose levels via a disproportionate increase in glucose rate of appearance (Ra) relative to glucose rate of disappearance (Rd). This may explain the fact that levels of plasma epinephrine, norepinephrine, and GH rise only transiently after a 10 s sprint (23) (see also 'Type of Exercise').

Hypoglycemia in the morning before exercise does not diminish the glycemia-raising effect of an afternoon sprint in young adults with T1D, suggesting that sprinting is a useful strategy for opposing hypoglycemia, regardless of prior hypoglycemia (34).

Types of exercise. Anaerobic efforts last only a short time (sometimes only seconds) but may increase the blood glucose level dramatically due to the release of the hormones epinephrine and glucagon. This rise in blood glucose is usually transient, lasting typically 30–60 min, and can be followed by hypoglycemia in the hours after finishing the exercise. Aerobic activities tend to lower blood glucose both during (usually within 20–60 min after the onset) and after the exercise (9). Peak insulin sensitivity in recovery appears to be approximately 7–11 h after the end of exercise in adolescents with T1D (35).

The impact of activity type upon short- and long-term glycemia is scrutinized by Tonoli et al. in a meta-analysis across all age groups (36). They concluded that repeated short sprints added to aerobic training can minimize the risk of hypoglycemia and that aerobic training (as opposed to resistance training, mixed or high-intensity exercise) is likely to improve chronic glycemic control.

Although not yet studied in the pediatric population, resistance-based exercise (i.e., weight training) produces less drop in glycemia compared with aerobic exercise (37) and if both activities are to be done in one setting, it may be preferable from a glycemic management standpoint to do the resistance activity before the aerobic activity (37), perhaps because of augmented growth hormone release (38).

Timing of the exercise. Morning activity, done before insulin administration, may not result in hypoglycemia as circulating insulin levels are typically low and glucose counterregulatory hormones may be high (39). Indeed, severe hyperglycemia may occur with vigorous exercise in these circumstances, even precipitating ketoacidosis if insulin has been withheld for a long period of time (40).

Conditioning. Patients frequently report that the drop in blood glucose may be less with regular conditioning

and familiarity with the sport, although no experimental evidence exists that tests this hypothesis. This may be because regular conditioning often is accompanied by a reduction in total daily insulin administration and a greater reliance on lipid as a fuel (41).

Degree of stress/competition involved in the activity. Catecholamines rise during high-intensity exercise, and their rise can contribute to exercise-associated hyperglycemia (42). The adrenal response during intense exercise or perhaps during stressful competition will raise blood glucose and may require corrective insulin administration (43).

Muscle mass/number of muscles used in the activity. Using more muscles during aerobic exercise produces a greater drop in blood glucose and weight-bearing activities tend to use more energy than non-weight-bearing activities.

Other factors involved in the glucose regulation during exercise

Metabolic control. Where control is poor and pre-exercise blood glucose level is high (>20 mmol/L), circulating insulin levels may be inadequate and the effect of counterregulatory hormones will be exaggerated, leading to a higher likelihood hyperglycemia and ketosis (40). In Ironman athletes with T1D, those with low (i.e., near normal) HbA1c had performance, equivalent to non-diabetic controls (44).

Blood glucose level. Some limited evidence exists to support a near normal blood glucose concentration during exercise for performance reasons. For example, high blood glucose has been found to reduce secretion of beta-endorphins during exercise, which has been associated with an increased rating of perceived exertion (RPE) during leg exercise (45). In fact, even baseline beta-endorphin levels were reduced in the diabetic subjects irrespective of blood glucose, and thus the resultant reduced tolerance of discomfort may compromise exercise performance in individuals with diabetes. Similarly, increases were found in RPE in adolescents with diabetes doing whole-body exercise (46), but the authors indicate that the higher response may be related to the lower peak mechanical power output often seen in these patients (47).

Even in well-controlled individuals, hyperglycemia at the time of exercise (adult study in controlled laboratory conditions) resulted in a shift from lipid to CHO oxidation (48).

Hypoglycemia has also been shown to compromise both sport performance and cognitive function in

youth with T1D (49). Thus a near normal glucose concentration may be optimal for overall sport performance.

Children with diabetes appear to have a normal aerobic and endurance capacity if good glycemic control is achieved (HbA1c <7.0%), even if they are slightly hyperglycemic at the time of exercise. In one study, physical working capacity in well-controlled prepubertal boys was not different from non-diabetic boys matched for age, weight, and physical activity patterns, even though the boys with diabetes exercised with considerably higher blood glucose concentrations (mean blood glucose 15 mmol/L at onset of exercise) (50). In line with this, cycling performances in adult males with T1D did not differ between glucose levels clamped at euglycemia vs. hyperglycemia (12 mmol/L, 220 mg/dL) (51). In contrast, aerobic capacity was lower and the fatigue rate higher in youth with T1D when glycemic control was less than optimal (i.e., HbA1c >7.5%) (26). Moreover, performance in sports like hockey, soccer, and sailing where a certain amount of cognitive function and precision is necessary may be better performed during normoglycemia compared with hyperglycemia, although studies have not yet been conducted to address this hypothesis. However, cognitive performance has been shown to be slower in youth with diabetes when their blood glucose is either hypoglycemic or hyperglycemic (52).

Type and timing of insulin injections. When regular (soluble) insulin has been injected prior to exercise, the most likely time for hypoglycemia will be 2–3 h after injection, when insulin levels peak. For rapid-acting insulin analogs, peak insulin action, and therefore the greatest hypoglycemia risk, is between 40 and 90 min (53).

It should be noted, however, that exercise can dramatically increase skin and systemic blood flow and insulin and glucose delivery to skeletal muscle (54). Exercise has been shown to increase rapid-acting insulin absorption rate (55), thereby likely hastening the peak insulin action. Basal insulin absorption, on the other hand, does not appear to be impacted significantly by long-acting insulin (glargine), although exercise can still promote a drop in glycemia compared with basal insulin injected at rest (56).

To help prevent hypoglycemia during prolonged exercise, reductions in bolus and/or basal insulin are typically required. The normal recommendation is to reduce rapid-acting analog prior to exercise lasting longer than 30 min. The impact of the scale of the reduction was studied in adults by Bracken et al. by reducing the pre-exercise insulin to 75, 50, or 25% of the normal dose. Interestingly, although the largest reduction was associated with higher

post-exercise glucose, there was no difference in the production of ketones (57). This is a reassuring message and is helpful when encouraging young people to experiment to find what scale of reduction works for them.

We have found no studies on the timing of basal insulins (NPH, glargine, or detemir) and exercise in children but Arutchelvam et al. found that insulin detemir was associated with less hypoglycemia during and post-exercise than insulin glargine (58).

When playing in morning or in all-day tournaments, a long-acting basal insulin given once daily in the evening can be substituted for one with shorter action (NPH) to reduce the basal insulin effect the next day while exercising. An alternative is to split the TDD in half and take half the long-acting basal insulin in the evening and then lower the second dose in the morning by 20–50% to compensate for the increased activity.

Type and timing of food. A meal containing CHOs, fats, and protein should be consumed roughly 3–4 h prior to competition to allow for digestion and to maximize endogenous energy stores (59). This is especially important for longer duration activities. Glycogen stores can be enhanced with a CHO beverage (1–2 g CHO/kg) approximately 1 h prior; this also helps to supplement energy stores and provide adequate fluids for hydration (60). As this CHO loading is insulin dependent, and this will not be covered by the preceding meal bolus, it might be reasonable to try giving 50% of the bolus that would be dictated by the insulin to CHO ratio at this time and monitoring the response. Next time, a little more or a little less insulin may be necessary based on the measured glucose response. While the experimental evidence is laid out above, it is often impractical to have a meal 3–4 h prior to exercise and 1–2 h is more likely. This makes the individualization via trial and error especially important.

If extra CHO is necessary for a short duration activity, then it may be useful to have ‘fast acting’ CHOs in a beverage form. An isotonic beverage containing 6% simple sugar (i.e., sucrose, fructose, and dextrose) provides optimal absorption compared with other more concentrated beverages with more than 8% glucose, such as juice or carbonated drinks that delay gastric absorption and cause stomach upset (60). One study, however, found that both 8 and 10% isotonic beverages were well-tolerated and helped to prevent the drop in blood glucose level during exercise in adolescents with T1D (61). The amount of CHO should be matched as closely as possible to the amount of CHO utilized during exercise, if a reduction in insulin is not performed. In general, approximately 1.0–1.5 g CHO/kg body weight/h should be consumed during exercise performed during peak insulin action in young adults

with diabetes (60), depending upon type of activity (see Table 2) (62). The requirements will be lower if the pre-meal bolus for the meal before the exercise is lowered or the exercise is performed several hours after the bolus dose has been given (0.3–0.5 g CHO/kg body mass/h).

Extra CHOs together with adjustments of insulin doses are especially important when the activity is of longer duration than 60 min (63). That CHO beverages perform best pre-exercise in minimizing the drop in blood glucose was affirmed by Dube et al. who studied a variety of nutritional strategies (breakfast and pre-exercise) in adolescents. They found that including protein in the breakfast (before morning exercise) was associated with less hypoglycemia during and after exercise (64).

Because insulin sensitivity remains elevated for hours post-exercise, CHO stores must be replenished quickly to lower the risk of hypoglycemia during the first few hours after the activity (CHO reloading).

Short duration and high-intensity anaerobic activities (such as weight lifting, sprints, board diving, and baseball) may not require CHO intake prior to the

activity, but may produce a delayed drop in blood sugar. For activities of these types, extra CHO after the activity may be needed.

Longer duration, lower intensity aerobic activities such as soccer (often described as a mixture between aerobic and anaerobic exercise), cycling, jogging, and swimming will require extra CHO before, possibly during and often after the activity.

Currently, no evidence-based guidelines exist on the amount and timing of increased CHO intake to limit post-exercise hypoglycemia. However, reductions in basal insulin, low-glycemic-index snacks (with no bolus), or reduced boluses at post-exercise meals will usually reduce the problem. A snack of complex CHO, fat, and protein at bedtime may limit nocturnal hypoglycemia caused by daytime exercise (65, 66).

Absorption of insulin.

Choice of injection site. As mentioned above, when an extremity (arm or leg) has been injected with insulin and is then exercised vigorously, the increased blood flow to the limb is likely to result in more rapid absorption and metabolic effect of the insulin (67). This may be especially marked if the injection site is hypertrophied. Thus, a cyclist may achieve more consistent response by choosing to inject in an arm or the abdomen rather than a leg before an event.

Ambient temperature. High temperature will increase insulin absorption and low temperature the converse (68). The latter may be a consideration in long distance swimming. Heat also induces additional stress on the cardiovascular system, resulting in greater energy expenditure and potential for a faster drop in blood glucose levels.

Altitude. There is likely to be no altitude effect on insulin during recreational activities such as piste skiing but de Mol et al. studied eight complication free young people with diabetes, climbing above 5000 m and found that despite high energy expenditure, insulin requirement increased. Further, they found that glucose levels (and insulin requirement) correlated directly with the symptoms of acute mountain sickness (69).

Most absorption studies were done with regular insulin. The effect is less pronounced with rapid-acting analogs (70). An intense 30-min period of exercise did not increase the absorption rate of glargine in adults with T1D (56).

Normal day-to-day exercise

Daily physical activities should be a part of the normal routine for both health benefits and for consistency in blood glucose management.

Table 2. Exercise exchanges of 100 kcal (420 kJ) in children of various body masses. Assuming that, on average, 60% of total energy is provided by carbohydrate, one exchange is equivalent to 60 kcal or 15 g carbohydrate

Activity	Body mass (kg)		
	20	40	60
Basketball (game)	30	15	10
Cross-country skiing	40	20	15
Cycling			
10km/h	65	40	25
15 km/h	45	25	15
Figure skating	25	15	10
Ice hockey (ice time)	20	10	5
Running			
8 km/h	25	15	10
12 km/h	—	10	10
Snowshoeing	30	15	10
Soccer	30	15	10
Swimming			
30 m/min breast stroke	55	25	15
Tennis	45	25	15
Walking			
4 km/h	60	40	30
6 km/h	40	30	25

Tables of carbohydrate intake guidelines for a variety of sports are provided in a recent review (62). This table shows the estimated number of minutes that a certain activity lasts to require 15 g of extra carbohydrate to keep the blood glucose from falling. For example, a 40 kg child should consume 15 g of carbohydrate for every 15 min of basketball, whereas a 60 kg child should consume 15 g of carbohydrate for every 10 min of basketball.

If the pre-meal or basal insulin dose is lowered, less extra carbohydrate than the table shows is probably needed.

The habitual physical activity of children encompasses activities performed during their leisure time as well as more structured activities in the framework of exercise, sports, or some school-related activities, such as physical education lessons. It was found that the spontaneous activity of children is by nature sporadic and intermittent, with bouts (95% of the time) of very intense activity not exceeding 15 s, and only 0.1% of active periods for more than 1 min (71). These activity periods are interspersed by rest periods that are shorter than 4 min. This particular form of spontaneous physical activity is deemed to be consistent with the biological needs of children (72) and necessary for their appropriate growth and development (71).

On average, at least 60 min of cumulative activity is recommended by most organizations with at least 20 min daily of vigorous activity. Guidelines also state that for health benefits, children (aged 5–11 yr) and youth (aged 12–17 yr) should minimize the time that they spend being sedentary each day (73). Sedentary time (i.e., screen time) is linked to elevated HbA1c levels in children and adolescents with T1D (74). Some groups of schoolchildren and teenagers with diabetes have been found to be more physically active than their non-diabetic friends (75) but others less so (76). In one recent study of children and adolescents with T1DM in Brazil increased physical activity was associated with the best glucose control (77), although this relationship between activity participation and glycemic control is not always found (74).

Regular and accustomed exercise is easier to manage because it is part of the daily routine. However, adjustments may still be necessary for sporadic extra physical activity.

Whatever level of involvement in exercise and sport that a child or adolescent with diabetes adopts, it is good practice to keep careful notes of what they do (i.e., timing and intensity of physical activity), what CHO has been taken and the blood glucose response before, during, and afterwards. Advice from the diabetes care team will be general in the first instance, but accurate record keeping will allow much more individualized and fruitful consultation. Emerging technologies, e.g., apps on Smartphones may have a role to play in improving record keeping.

Where exercise is performed regularly, insulin sensitivity is generally enhanced. A positive association between glycemic control (i.e., HbA1c) and aerobic fitness or reported physical activity exists in youth with T1D, suggesting that either increased aerobic capacity may improve glycemic control or that good metabolic control maximizes exercise (26, 28). An inverse relationship was observed between HbA1c level and the maximal work load in a study in diabetic

adolescents (78). The lack of evidence on improving HbA1c with exercise may be related to a tendency to reduce insulin doses too aggressively for exercise or the overconsumption of CHOs in an effort to avoid hypoglycemia (79).

Training

The management of diabetes may vary according to the phase of training so when endurance is being built with long moderate-intensity work, the insulin regimen and additional CHO may be quite different from that required when the concentration is on power and high-intensity training (80). See the 'Duration and intensity' section above for more detail on the possible effect of short, high-intensity work on glycemia.

Exercise causes enhanced muscle insulin sensitivity (81) and increased activation of non-insulin sensitive glucose transporters (GLUT-4) (22, 82). Insulin sensitivity was similar directly and 15 h after exercise but decreased to near untrained levels after 5 d in non-diabetic adults (83). During and immediately after exercise performed in the late afternoon and from 7 to 11 h in recovery, the insulin sensitivity is elevated in adolescents with T1D (35). In contrast, exercise performed earlier in the day results in heightened insulin sensitivity thought 11 h of recovery in adolescents with T1D, without an obvious biphasic response in sensitivity (84).

In practical life, exercise for >1 h appears to lead to increased insulin sensitivity and therefore an increased risk for hypoglycemia for 12–24 h (35), often occurring during evening after exercise (85). This may be because of several factors including the change in insulin sensitivity, a reduction in glucose counterregulation and the problem of a fixed basal regimen (86). This means that adolescents who only exercise on occasion can have real difficulties in managing their basal insulins. If hypoglycemia is frequent, then it may be better to limit vigorous exercise every other day rather than daily, if possible. If not, a strategy for altering basal insulins to cope with the widely varying insulin sensitivity is needed. Younger children more often exercise every day to some extent, which results in less post-exercise fluctuations in blood glucose.

Meals with high content of CHOs should be consumed shortly after the exercise event to take advantage of the period of heightened insulin sensitivity to help replenish glycogen content and limit post-exercise hypoglycemia. However, the insulin dose will need to be reduced (in relation to the normal insulin to CHO ratio for the individual) to avoid hypoglycemia. Adding protein to the post-exercise meal increases the glucose uptake and enhances

glycogen resynthesis in healthy individuals (64) (87). Added proteins will also stimulate the muscle recovery post-exercise.

It is well beyond the scope of this article to offer sport-specific training advice but such information is readily available – see:

- Diabetes Exercise and Sports Association (www.diabetes-exercise.org), an international organization that provides guidance and networking between novices, health professionals, and experienced diabetic athletes.
- www.runsweet.com where a combination of contributions from sportsmen and sportswomen are interspersed with expert advice.

Choice of insulin regimen

In developed health care environments, it is now the norm to commence insulin therapy with a multi-injection regiment or even an insulin pump. While for most children and adolescents, the choice of insulin regimen will not be influenced heavily by their exercise habits, for those who are regularly active either multiple daily injections or insulin pump therapy should be considered to allow for manipulations in insulin delivery prior to and following the activity.

In one small study of young adults with T1D, insulin pump usage was associated with better glycemic control in early recovery from vigorous exercise than MDI (i.e., less hyperglycemia) (88).

Twice daily injections

It may be difficult to maintain very strict blood glucose control on these regimens especially with different levels of exercise throughout the week, but the essential requirements of taking various forms of CHO before, during, and after exercise may be even more important than for more adjustable regimens. In these situations, tables of Exercise Carbohydrate equivalents may be a useful starting point (59).

Three injections insulin regimen

In these situations, normally a mixed insulin is given before breakfast, then a split-evening insulin regimen with rapid analog before the evening meal, and a longer acting insulin at bedtime. Again this regimen must be accompanied by appropriate CHO advice for moderate exercise, e.g., dancing or swimming two or three evenings per week or at weekends.

Multi-injection regimens or insulin pumps

These regimens afford greater flexibility for serious training and competitive events. Both pre-exercise

bolus and basal rates can be reduced before, during, and after exercise to help increase hepatic glucose production and limit hypoglycemia (see below).

A further variation is to use a long-acting insulin in conjunction with an insulin pump allowing partial replacement of the basal dose (once or twice daily long-acting injections) and therefore a longer period off the pump with lesser risk of ketosis.

The choice of insulin regimen is always influenced by many different factors including the availability of various insulins (and pumps), professional and personal expertise, and in the ideal world should be influenced by the nature of the sport. There is no doubt that being able to reduce the training day into manageable ‘chunks’ of 4–6 h makes control of blood glucose much more straightforward, with the potential to move training/competitive periods around in the day and being able to adjust the appropriate bolus (and perhaps basal) insulin doses (89). In general, if basal rates are to be reduced for exercise, then the reduction should occur approximately 90 min before the onset of the activity to allow the circulating insulin levels to drop sufficiently before the exercise starts (59).

Hypoglycemia

In adults, the autonomic and counterregulatory response to hypoglycemia the following day has been shown to be blunted by repeated episodes of low- or moderate-intensity exercise (90, 91). The same phenomenon is likely to be true for children. Glucose requirements for maintaining stable glucose levels in adolescents with diabetes are elevated during and shortly after exercise, as well as from 7 to 11 h after exercise (35). In adults, repeated episodes of hypoglycemia in a sedentary state result in an attenuated counterregulatory response to subsequent exercise and increases the risk for hypoglycemia. Hence, two to three times more exogenous glucose may be needed to maintain euglycemia during exercise following a previous exposure to hypoglycemia (92). In laboratory studies of diabetic adolescents who received their usual insulin dose and then performed 75 min walking on a treadmill, 86% had hypoglycemia if their starting blood glucose was less than 6.6 mmol/L (120 mg/dL). In the same study, it was noted that 15 g CHO was frequently insufficient to restore blood glucose to normal (93). In another study (94), 45% of children with T1D had blood glucose levels drop below 4.0 mmol/L (72 mg/dL) during 60 min of moderate cycling performed in the fed state when insulin was unadjusted for the activity. By consuming additional CHO (drinking 6–8% glucose solution) at a rate that equalled CHO utilization during exercise (approximately 1 g of CHO/kg body mass/h), the drop in blood glucose during exercise could be prevented (94).

The use of CGM and appropriate response to falling glucose may help to attenuate or avoid hypoglycemia during and after exercise (95).

If a child with diabetes is feeling unwell during exercise with signs and symptoms of hypoglycemia, glucose tablets or other form of quick-acting CHO should be given as for treatment of hypoglycemia, even if blood glucose cannot be measured to confirm hypoglycemia.

To treat hypoglycemia with a rise in BG of approximately 3–4 mmol/L (55–70 mg/dL), approximately 9 g of glucose is needed for a 30 kg child (0.3 g/kg) and 15 g for a 50-kg child. See the Hypoglycemia article for further advice and references.

On outward-bound or activity holidays all the responsible adults (and also peers) should be alert to the possibility of hypoglycemia. Strict guidance should be given that no person with diabetes should exercise or go off alone, or ‘decide’ not to have regular snacks when they are provided.

A sensible rule is that if young people with diabetes are together on holiday, they should stay in groups of at least four, so that two can accompany each other if they need to alert adult helpers to the occurrence of an accident or hypoglycemia.

Glucose tablets, glucose gel, or some form of rapidly absorbed sugar should always be carried by young people who exercise or, at a minimum, kept within a reasonable distance of the activity.

See Table 3 (96) for further advice on how to avoid hypoglycemia when exercising.

Late hypoglycemia

As mentioned above, hypoglycemia can occur several hours after exercise, especially when this has been prolonged and of moderate or high intensity (97). This is due to the late effect of increased insulin sensitivity and delay in replenishing liver and muscle glycogen stores and perhaps due to failed glucose counterregulatory hormone responses during the night (86). A single bout of exercise can increase glucose transport into skeletal muscle tissue for at least 16 h post-exercise in non-diabetic and diabetic subjects (30). In a controlled study, twice as many youngsters aged 11–17 yr had a hypoglycemic event on the night after an exercise day compared with the night after a sedentary day (when the basal overnight insulin was not altered) (85). CGM may be a valuable tool for determining the blood glucose response and hypoglycemia risk during and after exercise (98, 99). One adult study has shown that the likelihood of late hypoglycemia was greater after intermittent high-intensity than moderate-intensity exercise despite the blood glucose and catecholamine levels being higher after the former (31). Again in adults, use of CGMS in conjunction

Table 3. Summary recommendations for avoiding hypoglycemia in physically active young people with diabetes (adapted from reference 96)

-
- Arrive at a good level of metabolic control: neither with hyperglycemia nor ketonuria. Eventually measure blood glucose concentration before the activity.
 - Always carry some sugar.
 - Increase the intensity and duration of the activity in a progressive fashion.
 - In the few hours preceding the exercise, ingest slowly absorbing carbohydrates in order to replete the liver and muscle glycogen reserves.
 - In the case of unforeseen physical activity, increase glucose consumption immediately before, during, and after the activity
 - In the case of foreseen activity, decrease the insulin dose during and after intense muscular activity.
 - Do not inject the insulin at a site that will be heavily involved in the muscular activity.
 - When physical activity is planned at a time of peak insulin action, a marked reduction in the insulin dose should be made.
 - If the activity is of the prolonged endurance type, be certain to ingest glucose-sweetened water or carbohydrates just before, during, and after the exercise.
 - Measure the blood glucose before retiring on the evening after major physical activity, in order to avoid hypoglycemia during the night.
 - Evaluate the effect after every modification in insulin dose and every change in nutritional status.
 - Make the people accompanying you aware of the procedures and treatment of severe hypoglycemia (glucagon injection)
-

with a low-glucose suspend (i.e., threshold suspend) function on insulin pumps may reduce the duration and severity of hypoglycemia with exercise in laboratory conditions (100). It should be noted, however, that if a recent episode of exercise-associated hypoglycemia occurred, low-glucose suspend technology may not be as effective in ameliorating hypoglycemia risk (101).

Taplin et al. attempted to reduce hypoglycemia after a 60 min bout of exercise in 16 youths with T1D on insulin pumps by either reducing their basal insulin by 20% for 6 h or by giving 2.5 mg of oral terbutaline. Although the latter did reduce overnight hypoglycemia, it was associated with overnight hyperglycemia. The basal reduction was not only effective but also associated with some late high glucose results. The authors accept that reducing insulin in this way is not possible for patients using intermittent insulin injections (102).

Insulin adjustments

Competitive athletes may be tempted to reduce their insulin doses too much to avoid hypoglycemia and their metabolic control may suffer as a result (79). Careful monitoring and experiential adjustments are

essential. In a group of young people aged 10–18 yr, those attending a competitive sport of at least 6 h of exercise per week had a lower HbA1c (75).

In one study, cross-country skiers with T1D were able to carry on for several hours without hypoglycemia when reducing the pre-meal dose by 80%, compared with only 90 min if the dose was reduced by 50% (103). Some people find that lowering their pre-meal insulin dose may cause an initial rise in their blood glucose which impairs their performance. In such a case, it is probably better to rely on extra CHO intake just before the onset of exercise rather than dose reduction for best performance.

See Table 4 (104) for examples on adjustments of pre-exercise bolus doses in order to avoid hypoglycemia. There is a greater need for reduction of rapid-acting insulin when the dose is given within 1 h of the exercise, while the need of reduction is greater for later exercise (3 h post-meal) when using regular insulin. (53).

For evening exercise, it may be sensible to reduce the rapid analog before the evening meal by 25–75%, as well as taking 10–15 g of fast acting CHO before the activity.

Advice about reducing basal insulin by 10–20% (e.g., a reduction in overnight long-acting/basal insulin or basal rate in pump or reductions in subsequent mealtime boluses), and/or extra low glycemic index snacks following the activity is prudent.

With all-day or unusual activities such as camps, long-distance walking, skiing, water sports, etc. consider a 30–50% reduction of long-acting insulin the night before and on the day of the activity, or a 30–50% reduction in the pump's basal insulin throughout the day and the night following the activity. High excitement amusement parks and fairs may be more likely to raise BG because of adrenalin surges.

Table 4. Examples of percent reduction in pre-meal insulin bolus for a carbohydrate-containing meal, in order to strictly avoid hypoglycemia (with either pump or multiple daily injections) for low-, moderate-, and high-intensity exercise lasting 30 or 60 min in duration are given in the table. Note however, that this study was in adults and did not consider the effect of additional carbohydrate intake before or during the exercise. Moreover, the adjustments also were associated with an increased number of episodes of hyperglycemia pre-exercise and post-exercise (104)

Intensity of exercise	Duration of exercise and recommended reduction in insulin	
	30 min	60 min
Low (~25% VO ₂ max)	25%	50%
Moderate (~50% VO ₂ max)	50%	75%
Heavy (~75% VO ₂ max)	75%	—

%VO₂ max = percentage of maximal aerobic capacity.

It should be obvious from the above that individuals vary greatly in their response to different types of exercise so the most important thing is for patients and families to be aware of the broad themes and to use this knowledge coupled with good record keeping to find what works for them.

Insulin pumps

For certain types of exercise (like contact sports), it may be appropriate to disconnect prior to the start of the activity and remain disconnected for up to 1–2 h during an event. In these situations, patients may require a 50% bolus correction afterwards (i.e., 50% of the missed basal insulin while disconnected), if needed, to reduce any resulting post-exercise hyperglycemia. To get a significant lowering of the basal insulin effect during the exercise, the pump needs to be disconnected at least 60 min before starting the exercise (105), but many centers advise that the pump should not be disconnected for more than 2 h. The safer option may be to set a temporary basal rate 90 min before the activity (50–80% reduction depending upon the intensity and duration of the activity), lasting until the end of exercise.

Even if the pump is removed during exercise, hypoglycemia can still occur for several hours after the end of the activity (106).

After a short period of intense exercise ($\geq 80\%$ VO₂ max), marked catecholamine responses lead to hyperglycemia which lasts for approximately 2 h post-exercise in adults with T1D (43). Even when pre-exercise plasma glucose was normal, there ensued a post-exercise hyperglycemia which lasted for 2 h post-exhaustion in pump patients (107). This reaction may be exaggerated if the pump has been disconnected during the exercise. The rise in blood glucose may be prevented by giving a small additional dose of rapid-acting insulin at half-time or immediately after the exercise is finished, i.e., before the shower.

New insulin pump technology may offer better opportunities to avoid hypoglycemia associated with exercise. The ASPIRE study, considered the use of low-glucose suspend (LGS) technology to turn off an insulin pump for 2 h once a CGM sensor detected a blood glucose value less than 70 mg/dL (3.9 mmol/L). Subjects, including adolescents, were randomized to sensor augmented pump therapy with or without low-glucose suspend turned on in a crossover study. After overnight fasting, subjects exercised until hypoglycemia intervened. The LGS group duration of hypoglycemia was less (100).

In a further development, predictive low glucose management algorithms built into pumps are being designed to turn off the insulin delivery when the blood glucose reaches a certain point and turns it back

on again at a predetermined level. In *in silico* and live testing on adolescents exercising, this method delivered promising results with 80% of the experiments where the glucose fell below threshold resulting in the prevention of hypoglycemia (108).

Ketones

In situations of under-insulinization, whether through systematically poor control or intercurrent illness, any exercise is likely to be dangerous because of the effect of uninhibited action of the counterregulatory hormones. In one study in adults, patients exercising with a blood glucose of >20 mmol/L (260 mg/dL) and ketonuria experienced a rise in blood glucose over 40 min (109).

The rapid production of ketone bodies coupled with impaired muscle glucose uptake will lead not only to under-performance, but may precipitate ketoacidotic abdominal pain and vomiting. Thus it is important for families to be warned about not participating in exercise if blood glucose is high and ketones (small or more) are present in the urine (9, 89, 109) or the level of beta-hydroxybutyrate (BOHB, 'blood ketones') in blood is >0.5 mmol/L.

It is a relatively common misconception that no insulin is needed when prolonged exercise is to be undertaken. This could be a dangerous error unless insulin cover is being provided by a long-acting product, and under carefully monitored conditions.

Blood ketone testing (measuring BOHB) provides additional information to urine ketone testing (110). This method is excellent for rapid detection and exact measurement of ketone levels and is preferable, when available. During resolution of ketosis, blood BOHB normalizes sooner than urine ketones (111). Blood BOHB >0.5 mmol/L is abnormal in children with diabetes (112, 113).

Patients can be reassured that reducing insulin down to 25% of pre-exercise doses does not make later ketosis more likely (57).

What to eat and drink

When insulin is not reduced to accommodate for exercise, it is usually necessary to consume extra CHO in order to avoid hypoglycemia. This is dependent upon type and duration of activity.

The amount of CHO needed depends largely on the mass of the child and the activity performed as well as the level of circulating insulin (53). Up to 1.5 g CHO/kg of body mass/h of strenuous exercise may be needed.

Numerous charts indicating CHO replacement for specific exercises based on duration of activity and body size are found in references 114, 115 and for youth specifically in a review by Riddell and Iscoe (116).

The growing use of CGM may offer opportunities for better tailoring of food intake before, during,

and after exercise through the use of more precise algorithms (95).

It is worth reminding adolescents and young adults about the effect of alcohol upon the ability to respond to exercise and falling blood glucose (see chapters on Nutrition and Adolescence). Alcohol impairs the glucose counterregulation in subjects with diabetes by inhibiting gluconeogenesis (but not glycogenolysis) (117–120). Accordingly, hypoglycemia (especially night time) becomes more likely and is best avoided when participating in exercise, especially as alcohol may also impair performance.

While not confined to people with diabetes, the risk of dehydration should be borne in mind lest too much focus be kept upon glucose control. Even a 1% decrease in body mass due to dehydration may impair performance (121). In practice, both needs can often be met by using specially formulated drinks, but if dehydration is a risk, sugar free fluids should also be taken. Fluid intake should match sweat and hyperventilation losses, such that there is no change in body weight pre- versus post-exercise. Fluid intake may need to be as great as 1.3 L/h in adolescents exercising in hot and humid environments (122).

Monitoring

Blood glucose monitoring is the key for the active child with diabetes so that trends in glycemic responses can be identified. Records should include notes of their blood glucose, the timing, duration, and intensity of exercise, as well as the strategies used to maintain glucose concentrations in the normal range. Measurements of glucose should be taken before, during, and after the end of exercise with particular attention paid to the direction of change in glycemia.

It can be especially useful, where a young person is involved in multiple sports or different types of training/competition for them to keep records in a structure that allows similar elements (e.g., all the gym sessions or competition days) to be looked at together.

Monitoring several hours after exercise and before bed is particularly critical on days where strenuous activities occur, as nocturnal hypoglycemia is common. It remains controversial whether certain bedtime BG levels predict nocturnal hypoglycemia and predictions are particularly difficult after exercise. In one hospital-based study where 34% had night-time hypoglycemia using a twice daily regimen NPH as basal insulin, a bedtime blood glucose of less than 7 mmol/L (125 mg/dL) suggested particular risk for nocturnal hypoglycemia (123), while another study using long-acting basal analogs or pumps found a lower frequency of 13% but no threshold for nocturnal hypoglycemia risk after exercise in the afternoon (85).

CGM has proven to be a valuable adjunct to blood glucose monitoring in both the prevention and early detection of exercise-induced hypoglycemia (98, 99) and during a sports camp detected significantly more episodes of hyperglycemia and hypoglycemia than frequent blood glucose testing (124). With CGM it was also shown that exercise-induced hypoglycemia could be reduced by using value and trend information along with a new CHO intake program (95).

Caution should be taken when using BG meters in extreme temperatures (125). Meters using glucose dehydrogenase may give more accurate readings at high altitude. In circumstances where control solution is used to check the meter, e.g., on a long hike, further criteria apply with the solution only being accurate between 15 and 30°C. In cold environments such as skiing, keeping a meter and strips inside several layers of clothes close to the body will usually avoid inaccurate readings.

Special care should be taken at high altitude where the symptoms of hypoglycemia may be confused with those of hypoxia/altitude sickness. Taking acetazolamide to prevent or treat altitude sickness may contribute to an increased risk of ketoacidosis in a person with diabetes (126). However, in another report, 73% of the participants with diabetes used acetazolamide without side effects (127).

School activities and diabetes camps

While this article is aimed principally at the practicalities of managing intense and/or prolonged physical activity, it is clear that the advice can be tailored for more moderate exercise. In the normal school week, most young people will have at least one period of physical education, and how they deal with avoiding hypoglycemia will be dependent upon all of the factors mentioned above.

Some earlier studies have shown that school time may be one of the highest providers of activity to youth (128–131). This is particularly relevant as the school environment has the potential to encourage physical activity in youth through physical education lessons, extracurricular activities (structured physical activity), and during recess or lunchtime (discretionary physical activity).

For many, all that will be required for a 30 min recess break is a small snack of 10–15 g CHO, e.g., a fruit or fruit juice, dried fruit, a cereal, fruit or granola bar or sports bar. This may also be a convenient opportunity to allow a treat such as chocolate or a few sweets. Chocolate contains fat which will cause the sugar to be absorbed more slowly (132). This can make it more suitable for low-grade longer-lasting activity, e.g., hiking, swimming, or long walks. However, the extra calories will not benefit a child with weight problems.

Where a multi-injection regimen or a pump is being used, a reduction in the pre-exercise bolus or setting a temporary basal rate may be appropriate (see Table 3 below).

For pump patients, a short period of disconnection may be best to allow free activity.

For longer periods of physical activity (>60 min), a reduction in basal insulin by 30–50% should be considered, along with CHO snacks being provided.

Activity weeks are now a common part of the school curriculum and many young people with diabetes also have the opportunity to attend dedicated diabetes camps. These two situations differ mainly in the expertise available, with the latter usually being managed and monitored by diabetes professionals with advice about adjustments of insulin and food on-site.

Clinical professionals can gain much more insight into the day-to-day management of diabetes by participating in diabetes camps and in some countries this is now a training requirement.

The benefits of spending a week being active in the open air are obvious and self-esteem is often improved, and where the activity is shared with others with diabetes, there are real opportunities to learn better ways of coping. Camps for children with diabetes that include counseling on nutrition and insulin adjustments for exercise can result in improved glycemic control (133–135).

Insulin doses may have to be reduced substantially to prevent hypoglycemia in a camp setting, especially in children not accustomed to physical activity, and it is wise to begin with a 20–25% reduction in TDD (136). A more recent study by Miller et al. was conducted on 256 children aged 7–15 yr attending a week long summer camp (137). They reduced all children's insulin by 10% (55% were on pumps). Sixty percent of them had at least one episode of hypoglycemia on the first day. While, overall, insulin doses did not decrease further during the camp, the number of hypoglycemic episodes decreased. There was a difference between pumps and injections with children using injections requiring around an extra 8% reduction. They also noted that the older children were more likely to have hypoglycemic episodes. So it would seem that consideration of these factors may be wise before recommending the scale of insulin reduction.

When being physically active for a prolonged period, for example, on a skiing trip or an outward bound camp, insulin sensitivity will increase after 1–2 d which will probably call for substantially lowered insulin doses (decreased by 20% or sometimes even 50%, especially if not used to hard physical exercise). The increased insulin sensitivity will continue for at least a couple of days after returning home (81).

Where young people will be cared for by non-clinical professionals (e.g., teachers), it is vital that

both the adults and the child/adolescent are provided with appropriate verbal and written information as well as emergency contact telephone numbers.

The emergence of 'cloud technology' will afford even better opportunities to support children and young people participating in camps and activities away from home but care will be required not to overstep and impinge upon the development of independence.

Special mention should be made of the need to plan ahead. Activities often last longer than anticipated so extra snacks and hypoglycemia remedies should always be carried. Diabetes educators may meet with parents, school, and support staff to ensure that a child's participation can be planned properly.

While very rare, it may occasionally be advisable for a diabetes team to recommend to a school that a young person should not go on a school activity week. For example, safety might be compromised if the person with diabetes has exhibited dangerous behavior such as frequent omission of insulin or episodes of disabling hypoglycemia. The negative experience from handling a difficult child and the impact upon the others in the group might prejudice the prospects for future children with diabetes.

Miscellaneous advice for unusual activities

Everything possible should be done to support a young person with diabetes who has serious sporting aspirations, or simply wants to understand how best to manage their control while participating. However, diabetes care teams have a duty of care and there are occasions when medical 'certification' is required before participation is allowed. Examples include diving and boxing. It would be negligent to provide such certification without careful consideration of the overall control and knowledge of the participant, as well as the possible impact of any other health factors such as diabetes complications. It may be possible to use a little leverage here to persuade the young person that it is in their interest to work with the team to improve their self-management.

Participation in almost any sport or exercise is likely to be safer in company, but for the person with diabetes this is even more important. At very least, one companion should know something about diabetes and how to recognize and manage hypoglycemia. Every participant in a sports team should be aware of a person with diabetes and know where to find the person's hypoglycemia remedies.

It is good practice to have 'Diabetes ID' somewhere on the body – preferably in the form of a durable bracelet or necklace.

Taking account of diabetes in other extreme situations may be lifesaving, e.g., the signs and symptoms of exhaustion and hypothermia could easily be

confused with hypoglycemia. It is always safer to assume that the latter is making some contribution and to check blood glucose or treat expectantly.

Diving clubs in the UK, as well as in many other countries, have allowed individuals with diabetes to dive under certain carefully controlled circumstances (138), while in Australia, New Zealand, and Norway, only people with diet-controlled diabetes are allowed to dive (139). The suggested age limit in the UK is ≥ 18 yr (≥ 16 yr if taking part in a special training program) (140). In the USA, the same age limits apply, and teenagers are only allowed to dive after counseling by a physician and with letter stating they understand how to care for their diabetes during a dive. This letter is usually only provided to teenagers diving with their parents and after completing diving certification (140) (<http://www.diversalertnetwork.org/news/download/SummaryGuidelines.pdf>). In all countries where recreational scuba diving is allowed when diagnosed with T1D, the individual has to be declared as 'fit to dive' by a physician and this should also be continuously reevaluated (140). Specifically, the individual should have had no severe hypoglycemic episodes in the last 12 months.

A large number of dives performed by individuals with diabetes has been reported where no deaths, episodes of decompression illness, or hypoglycemia occurred (141), even in 16- to 17-yr old adolescents (142). In another report, hypoglycemic events were present in very small numbers, with no adverse outcome (143). Divers Alert Network (DAN) found 1.5% of participants having diabetes in a group of 1180 divers in Project Dive Exploration (144). In this report, 4 of 101 accidents involved diabetes that could indicate that individuals with diabetes are exposed to a higher risk than healthy individuals.

Repetitive episodes of hypoglycemia should be avoided during days before diving, as this could blunt the hormonal response during subsequent exercise or hypoglycemia (92).

The use of downloaded data regarding 2 wk of home glucose measurements made it possible to detect those who are suitable for diving.

In order to prevent episodes of hypoglycemia during the dive, a monitoring schedule is recommended with assessment of glucose levels via finger pricking 60, 30, and 10 min pre-dive and immediately post-dive (145). The same result was found when analyzing data from a CGM before, during, and after dive (146).

Those individuals with T1D who are permitted to dive should be trained to signal 'L' (low) for hypoglycemia (signal performed with the hand while diving). For safety reasons they should also be trained to use a fructose/glucose gel for oral ingestion below the surface, if signs of hypoglycemia are present during dive (146).

Type 2 diabetes

As opposed to the situation in T1D, there is no question that exercise has a direct and important part in the treatment of T2D. Exercise results in changes in body composition, reducing the amount of fat and increasing the amount of lean tissue: muscle, fibers, and bone. This increases the metabolic rate, reduces blood pressure and low-density lipoprotein (LDL) cholesterol, and increases high-density lipoprotein (HDL), reducing the risk of cardiovascular morbidity and mortality (147). The vast majority of studies on T2D and exercise have been done in adults, but there is every reason to believe that the results are applicable to adolescents as well.

Affected individuals and family members of adolescents in whom T2D has been diagnosed have lifestyles characterized by minimal physical activity (148) and fitness (149).

A twice-per-week 16-wk resistance training program significantly increased insulin sensitivity in overweight adolescents independent of changes in body composition (150).

Large clinical trials in adults with impaired glucose tolerance demonstrate that lifestyle interventions including exercise can reduce the incidence of T2D (151).

In a meta-analysis it was found that exercise training reduced HbA1c by an amount that should decrease the risk of diabetic complications. This effect was not mediated primarily by weight loss (152).

The incidence of hypoglycemia in T2D is lower than in T1D, partly because counterregulatory mechanisms are much less affected, but patients taking insulin or sulfonylurea medication (especially long-acting preparations) may require reduction in doses (153, 154).

Diabetes complications

Competitive sports are generally safe for anyone with T1D who is in good metabolic control and without long-term complications (155). However, patients who have proliferative retinopathy or nephropathy should avoid exercise conditions that can result in high arterial blood pressures (systolic pressures >180 mm Hg), such as lifting heavy weights (or any tasks in which a Valsalva manoeuvre is involved) or performing high-intensity sprints (156) or a cold bath after a sauna. Patients with complications should be monitored with ambulatory blood pressure measurement during exercise. Patients with peripheral neuropathy should be careful to avoid blisters and cuts and should avoid running and other sports that involve excessive wear of legs and feet (156). See reference 155 for more detailed advice on diabetes complications and exercise, and (157) for a more complete lists of sport-specific advice.

Diabetes and bone

The relationship between diabetes and osteopenia has been known since the 1950s but there has been much conflicting evidence. More recent studies have confirmed that children and adolescents with T1D do appear to have reduced bone mineral density compared with their non-diabetic peers (inversely correlated with HbA1c) (158). Whether or not this is, in turn, influenced by physical activity is interesting given the widespread evidence that children generally are not meeting the published targets for activity. Salvatoni et al. (159) studied 57 children and adolescents with diabetes and 57 controls and followed them with accelerometers to assess activity. Like others, they found that bone mineral density was less in diabetes but they also found a direct correlation between the average time per week spent doing physical activity and bone mineral content. Their findings were confirmed by Heilman et al. (160) who found the most significant reductions in bone mineral content and bone mineral density in boys with diabetes and that the boys were also the least active.

Contrary evidence was presented in 2010 by Maggio et al. who found that bone mineral density was normal during growth in 32 children with diabetes but that markers of bone turnover were decreased (161). Further support for abnormal bone metabolism in diabetes was demonstrated by Hamed et al. in 2011 when they studied 36 children and adolescents with diabetes and 15 controls and found that the group with diabetes had higher phosphate and parathyroid hormone levels with significantly lower levels of calcium, IGF-1, and 25(OH)D. They also showed total body osteopenia-osteoporosis in 94.4% (total body) (162).

A prospective study by Maggio et al. in 2012 looked at the impact of two 90 min sessions per week of weight-bearing exercise for 9 months (ball games, jumping, rope-skipping, and gymnastics) upon bone mineral density in 27 diabetic and 32 healthy children (163). After the intervention the cohort of diabetic and healthy children randomized to exercise had similar measures of bone mineral density and these were significantly different from the non-intervention group.

Conflicts of interest

The authors have declared no conflicts of interest.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Management of children and adolescents with diabetes requiring surgery

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

Glycemic targets for surgery

Aim to maintain blood glucose in the range of 5–10 mmol/L (90–180 mg/dL) during surgical procedures in children (C).

Presurgical assessment

- Presurgical assessment should be done several days before surgery to allow for an assessment of glycemic control, electrolyte status, and ketones (urine or blood) (E).
- If glycemic control is known to be poor and surgery is not urgent, delay the procedure until glycemic control has improved. If surgery cannot be delayed, consider admission to the hospital before surgery for stabilization of glycemic control (E).

Preoperative care for children with type 1 or type 2 diabetes treated with insulin

Children and adolescents with type 1 or type 2 diabetes treated with insulin:

- Must be admitted to the hospital if receiving general anesthesia (GA) (E).

- Should be scheduled as the first case of the day (E).
- Need insulin, even if fasting, to avoid ketoacidosis (A).
- May initially receive an intravenous (IV) infusion without dextrose for minor surgery or procedures (lasting for less than 2 h) if treated with basal/bolus insulin regimen or continuous subcutaneous insulin infusion (CSII) (C).
- Should initially receive an IV infusion with dextrose for major surgery or procedures (lasting for at least 2 h) or if treated with NPH insulin (E).
- Require careful blood glucose monitoring before the procedure to detect hypoglycemia and hyperglycemia (E).
- Should coordinate the timing of preoperative food and fluid restrictions with the anesthetist (E).
- Require specific adjustment of their insulin schedule depending on the type of surgery (major or minor), the patient's insulin regimen, and the time of the surgical procedure (morning or afternoon) (E).

Intraoperative care

- Monitor blood glucose concentration at least hourly during and immediately after GA (E).

- Use an IV infusion with dextrose during any major surgery (lasting for at least 2 h) or for patients treated with NPH insulin (E).
- Use an IV infusion initially without dextrose during minor surgery or procedures (lasting for less than 2 h) if treated with basal/bolus insulin regimen or CSII (C).
- Adjust dextrose infusion and insulin to maintain blood glucose in the range 5–10 mmol/L (90–180 mg/dL) (C).
- If there is an unexpected acute drop in blood pressure, normal saline (NS) (0.9% NaCl) or Ringer's lactate must be infused rapidly. In this circumstance, potassium-containing fluids must *not* be infused rapidly (E).

Postoperative care

- Once the child is able to resume oral nutrition, resume the child's usual diabetes treatment regimen. Give short- or rapid-acting insulin (based on the child's usual insulin:carbohydrate ratio and correction factor), if needed, to reduce hyperglycemia or to match food intake. (E)

Special situations

Emergency surgery (E). Before emergency surgery, always check blood glucose, blood β -hydroxybutyrate (if available) or urinary ketone concentration, serum electrolytes, and blood gases if ketone or blood glucose levels are high. If ketoacidosis is present, follow an established treatment protocol for diabetic ketoacidosis and delay surgery, if possible, until circulating volume and electrolyte deficits are corrected. If there is no ketoacidosis, start IV fluids and insulin management as for elective surgery.

Type 2 diabetes patients on oral medication alone.

- Discontinue metformin 24 h before major surgery (lasting at least 2 h) and on the day of surgery for minor surgery (C).
- Discontinue sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, and Glucagon-like peptide-1 (GLP-1) analogs on the day of surgery (E).
- Patients undergoing a major surgical procedure expected to last at least 2 h should be started on an IV insulin infusion as described above (E).

General recommendations

- Whenever possible, surgery on children and adolescents with diabetes should be performed in centers with appropriate personnel and facilities to care for children with diabetes (E).

- To ensure the highest level of safety, careful liaison is required between surgical, anesthetic, and children's diabetes care teams before admission to the hospital for elective surgery and as soon as possible after admission for emergency surgery (E).
- Centers performing surgical procedures on children with diabetes should have written protocols for postoperative management of diabetes on the wards where children are admitted (E).

The management of diabetes in children now includes a wide array of insulin analogs, insulin delivery devices, and regimens. Safe management of the child with diabetes in the perioperative period requires not only an understanding of the pathophysiology of the disease but also a thoughtful consideration of each child's specific diabetes treatment regimen, glycemic control, intended surgery, and anticipated postoperative course. Therefore, it is essential that the surgeon and anesthesiologist liaise with the child's diabetes team prior to any planned surgery. Evidence-based controlled studies of perioperative care specifically for children with diabetes are lacking.

The current, revised guidelines are based on the 2009 ISPAD Consensus Guidelines (1). They are also informed by The National Evidence-Based Clinical Care Guidelines for Type 1 Diabetes for Children, Adolescents, and Adults from the Australasian Paediatric Endocrine Group and Australian Diabetes Society (2), the Canadian Diabetes Association: Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (3), and the Association of Children's Diabetes Clinicians Care of Children under 18 yr with Diabetes Mellitus Undergoing Surgery (4). They include recommendations from a recent comprehensive review of perioperative management for children with diabetes published in the anesthesiology literature (5). Because there are few relevant scientific papers on management of children during surgery, the recommendations are mostly based on expert opinion. Where appropriate, guidelines for perioperative management of adults with diabetes are also used to inform these recommendations.

Glycemic targets for surgery

The appropriate glycemic targets during the perioperative period remain controversial. The stress of surgery leads to a complex neuroendocrine stress response characterized by hyperglycemia and a catabolic state. To achieve optimal glycemic control, insulin dosage may need to be increased on the day of major surgery and for approximately 2 d after surgery (6). Hyperglycemia has been associated with an increased risk of postoperative infection (7).

In a study of 23 000 patients in 1973, adults with diabetes had an approximately 10-fold increased risk of postoperative wound infections (8). However, a recent systematic review of the adult literature found insufficient evidence to support strict glycemic control versus conventional management for the prevention of surgical site infections (9).

A recent meta-analysis showed that adult patients in surgical intensive care units (ICUs) appear to benefit from intensive insulin therapy and tight glycemic control, whereas patients in other ICU settings may not (10). Therefore, a consensus statement from the American Association of Clinical Endocrinologists and American Diabetes Association (11) recommends that an insulin infusion should be used to control hyperglycemia in the majority of critically ill patients in the ICU setting, with a starting glycemic threshold of no higher than 10 mmol/L (180 mg/dL). Once intravenous (IV) insulin therapy has been initiated, blood glucose should be maintained between approximately 8 and 10 mmol/L (140 and 180 mg/dL). Without prospective data from randomized controlled trials to establish specific guidelines in non-critically ill patients treated with insulin, premeal glucose targets should generally be <8 mmol/L (140 mg/dL) and random blood glucose values <10 mmol/L (180 mg/dL) as long as these targets can be safely achieved.

Few pediatric trials to date are available to inform these ranges and are limited to the critical care setting (12, 13). Vlasselaers et al., for example, showed shorter length of stay, attenuated inflammatory response, and decreased mortality in patients randomized to targeting of age-adjusted normoglycemia (14); however, the rate of severe hypoglycemia (<40 mg/dL, <2.3 mmol/L) was 25%. More recently, Macrae et al. conducted a multicenter trial in 13 centers in England involving critically ill children in pediatric ICUs (15). Tight glycemic control did not have a significant effect on major clinical outcomes and was, again, associated with a higher rate of hypoglycemia than conventional glucose control. In a systematic review and meta-analysis of the four randomized clinical trials of tight glycemic control with intensive insulin therapy in critically ill children, Srinivasan and Agus (13) reported that, while acquired infection was reduced, there was no decrease in 30-d mortality and a higher incidence of hypoglycemia was observed. Similarly, a systematic review and meta-analysis of 12 randomized trials in adults found intensive blood glucose control in the perioperative period did not significantly improve postoperative outcomes but was associated with a risk of hypoglycemia in *post-hoc* analyses (16).

Appropriate perioperative glycemic targets for minor surgical procedures are less clear. However, studies in adults that compared different methods of

achieving glycemic control during minor and moderate surgery did not demonstrate any adverse effects of maintaining perioperative glycemic levels between 5 and 11 mmol/L (~90–200 mg/dL) (17–19).

Therefore, based on the available data, it seems reasonable to aim for blood glucose in the range of 5–10 mmol/L (90–180 mg/dL) during surgical procedures in children. However, the benefits of tightening glycemic control must be weighed against the risk of perioperative hypoglycemia, which may not be recognized during anesthesia. This risk can be mitigated, however, by frequent intra- and post-operative blood glucose monitoring.

Classification of procedures and presurgical assessment

In the management of children with diabetes undergoing surgery it is helpful to divide procedures into two categories:

Minor surgery

Minor surgery requires brief general anesthesia (GA) (or heavy sedation), usually of less than 2 h duration, and should not have a major impact on glycemic control. Examples include common day surgery procedures: endoscopies, duodenal biopsy, adenotonsillectomy, grommet insertion, and simple orthopedic procedures.

The child will usually be discharged from the hospital on the day of the procedure. Likewise, repeated minor procedures performed on hospitalized patients receiving treatment for cancer or patients with severe burns are of short duration (e.g., dressing changes) and may also be considered minor.

Major surgery

Major surgery requires more prolonged GA, is associated with greater risks of metabolic decompensation, and the child is unlikely to be discharged from the hospital on the day of the procedure. These surgeries are typically expected to last for at least 2 h.

Whenever possible, surgery should be performed when diabetes is under optimal control. If circumstances permit a presurgical assessment, this should, ideally, be done several days before the surgery to allow for an assessment of glycemic control, electrolyte status, and ketones (urine or blood). If glycemic control is known to be poor and surgery is not urgent, the procedure should be delayed until glycemic control has improved. If glycemic control is uncertain or poor and surgery cannot be delayed, consider admission to the hospital prior to surgery for assessment and stabilization of glycemic control.

Preoperative care for children with type 1 or type 2 diabetes treated with insulin

Children and adolescents with type 1 or type 2 diabetes treated with insulin:

- Must be admitted to the hospital if receiving GA.
 - In cases with documented good control, it should be possible to admit early on the day of surgery for both minor and major procedures. Otherwise, it is preferred to admit in the afternoon before surgery to give time for correction of metabolic status overnight.
- Should be scheduled as the first case of the day.
- Need insulin, even if fasting, to avoid ketoacidosis.
- May initially receive an IV infusion without dextrose for minor surgery or procedures (lasting for less than 2 h) if treated with basal/bolus insulin regimen or continuous subcutaneous insulin infusion (CSII).
- Should initially receive an IV infusion with dextrose for major surgery or procedures (lasting for at least 2 h) or if treated with NPH insulin.
- Require hourly capillary blood glucose monitoring to detect hypoglycemia and hyperglycemia before the procedure. If the blood glucose exceeds 14 mmol/L (~250 mg/dL), a conservative dose of rapid-acting insulin or short-acting insulin (regular) should be administered to restore blood glucose to the target range.
- Should coordinate the timing of preoperative food and fluid restrictions with the anesthetist.
 - The usual recommendation is no solid food for at least 6 h before surgery (20). Clear fluids (and breast milk) may be allowed up to 4 h before surgery (check with anesthetist).
- Require specific adjustment of the insulin schedule depending on the type of surgery (major or minor), the patient's insulin regimen, and the time of the surgical procedure (morning or afternoon). Guidelines for each scenario are presented.

Major surgery (as defined above)

- On the evening before surgery:
 - Give the usual evening and/or bedtime insulin(s) and bedtime snack.
 - Monitor blood glucose and measure blood β -hydroxybutyrate (BOHB) or urinary ketone concentration if blood glucose is >14–20 mmol/L (>250–360 mg/dL).
- Omit the usual morning insulin dose.
- At least 2 h before surgery, start an IV insulin infusion [e.g., dilute 50 units regular (soluble) insulin in 50 mL normal saline, 1 unit = 1 mL] and provide

IV maintenance fluids consisting of 5% dextrose and half-normal saline (0.45% NaCl) (see Table 1).

- Monitor blood glucose levels at least hourly before surgery and as long as the patient is receiving IV insulin.
- Aim to maintain blood glucose between 5 and 10 mmol/L (90–180 mg/dL) by adjusting the IV insulin dose or the rate of dextrose infusion during surgery.
- When oral intake is not possible, the IV dextrose infusion should continue for as long as necessary.

Minor surgery (as defined above)

Algorithms for different types of insulin regimens are suggested below. For more detail, see reference (5).

- (i) Patients treated with twice daily basal (NPH, insulin detemir, or insulin glargine) and rapid- or short-acting insulins:

- Morning operations

- On the morning of the procedure, give 50% of the usual morning dose of intermediate-acting insulin (NPH) or the full usual morning dose of long-acting insulin (detemir or glargine). With premixed insulin, give only 50% of the equivalent dose of the basal (NPH) component.
- Omit the short- or rapid-acting insulin unless it is needed to correct hyperglycemia.
- Commence IV fluids containing dextrose 5–10%, as necessary, to prevent hypoglycemia.
- Alternatively, IV insulin infusion may be started as described above.

- Afternoon operations (if unavoidable)

- On the morning of the procedure, give 50% of the usual dose of intermediate-acting insulin (NPH) or the full usual morning dose of long-acting insulin (detemir or glargine). With premixed insulin, give only 50% of the equivalent dose of the basal component (NPH).
- The dose of short- or rapid-acting insulin will depend on whether the child is permitted to eat breakfast.
- Alternatively, give 30–40% of the usual morning insulin dose of short- or rapid-acting insulin (but no intermediate- or long-acting insulin) and use an IV insulin infusion beginning at least 2 h before surgery (Table 1).

Table 1. Infusion guide for surgical procedures

(i) Maintenance fluid guide

- Dextrose (for major surgery and any surgery when NPH has been given) 5% dextrose; 10% if there is concern about hypoglycemia. If blood glucose is high (> 14 mmol/L, 250 mg/dL), use half-normal saline (0.45% NaCl) without dextrose and increase insulin supply but add 5% dextrose when blood glucose falls below 14 mmol/L (250 mg/dL).
- Sodium
There is evidence that the risk of acute hyponatremia may be increased when hypotonic maintenance solutions (i.e., <0.9% NaCl) are used in hospitalized children (27). Many centers, therefore, use saline 0.45–0.9% (77–154 mmol Na/L). A compromise would be to give 0.45% saline with 5% dextrose, carefully monitor electrolytes, and change to 0.9% saline if plasma Na concentration is falling.
- Potassium
Monitor electrolytes. After surgery, add potassium chloride 20 mmol to each liter of intravenous fluid. Some centers add potassium routinely only if infusion is required for more than 12 h.

Example of calculation of maintenance requirements:

	Body weight (kg)	Fluid requirement per 24 h
For each kg between	3–9	100 mL/kg
For each kg between	10–20	Add an additional 50 mL/kg
For each kg over	20	Add an additional 20 mL/kg
(Maximum 2000 mL female, 2500 mL male)		

(ii) Insulin infusion

- Add soluble (regular) insulin 50 units to 50 mL normal saline (0.9% NaCl), making a solution of 1 unit insulin/mL; attach to syringe pump and label clearly
- Start infusion at 0.025 mL/kg/h (i.e., 0.025 U/kg/h) if blood glucose is <6–7 mmol/L (~110–140 mg/dL), 0.05 mL/kg/h if 8–12 mmol/L (~140–220 mg/dL), 0.075 mL/kg/h between 12 and 15 mmol/L (~220–270 mg/dL) and 0.1 U/kg/h if >15 mmol/L (~270 mg/dL).
- Aim to maintain blood glucose between 5 and 10 mmol/L (90–180 mg/dL) by adjusting insulin infusion hourly
- Blood glucose must be measured at least hourly when the patient is on IV insulin
- **Do not stop the insulin infusion** if blood glucose <5–6 mmol/L (90 mg/dL) as this will cause rebound hyperglycemia. Reduce the rate of infusion.
- The insulin infusion may be stopped temporarily if blood glucose is <4 mmol/L (55 mg/dL) but not >10–15 min.

IV, intravenous.

- If the anesthetist allows the child to eat a light breakfast and to consume clear liquids up to 4 h before the procedure, IV fluid administration (and IV insulin infusion, if applicable) should commence 2 h before surgery or no later than midday (Table 1).

(ii) Patients treated with once daily basal/bolus insulin regimens:

Children on basal/bolus regimens benefit from not discontinuing their basal insulin before minor surgical procedures. This is particularly relevant for children requiring repeated procedures.

• Morning operations

- On the morning of the procedure, give the usual dose of long-acting insulin (glargine or detemir) if usually given at this time. If preoperative evaluation shows a pattern of low blood glucose values in the morning, consider reducing the dose of long-acting insulin by 20–30%.
- Omit the short- or rapid-acting insulin unless needed to correct hyperglycemia.
- Commence IV fluids. Patients with a normal blood glucose may initially utilize IV fluids without

dextrose. With an appropriately titrated basal rate and careful monitoring, this approach may be more physiologic (21, 22).

- Alternatively, IV insulin infusion may be started as described above.

• Afternoon operations (if unavoidable)

- On the morning of the procedure, give the usual dose of long-acting insulin (if usually given at this time).
- If allowed to eat breakfast, give the usual dose of rapid-acting insulin or 50% of the usual short-acting insulin.
- If the anesthetist allows the child to eat a light breakfast and to consume clear liquids up to 4 h before the procedure, IV fluid administration (and IV insulin infusion, if applicable) should commence 2 h before surgery or no later than midday (Table 1).

(iii) Patients treated with CSII:

- If possible, and provided the anesthetist agrees, use of CSII may be continued during a surgical procedure. If the anesthetist is not confident with CSII (pump) management, it is safest to remove the

insulin pump and substitute an IV insulin infusion to deliver insulin, as described above.

- When a child on CSII goes to the operating theatre, it is important to secure the subcutaneous infusion cannula to prevent dislodgement and interruption of insulin delivery during the procedure.
- If the GA is short (<2 h), the pump can continue to infuse insulin at the basal rate appropriate for the time of day.
 - Basal rate can be suspended, if necessary, for no more than 30 min to correct any episodes of mild hypoglycemia.
- Do not give a bolus dose of rapid-acting insulin unless necessary to correct hyperglycemia.
- Commence IV fluids. Patients with a normal blood glucose may initially utilize IV fluids without dextrose. With an appropriately titrated basal rate, this approach may be more physiologic (21, 22).
- Alternatively, IV insulin infusion may be started as described above.

Intraoperative care

Surgical stress may cause hyperglycemia and increased insulin requirements. Anesthesia may cause vasodilatation and drop the blood pressure. Therefore, blood pressure should be carefully monitored.

Monitor blood glucose measurements at least hourly during and immediately after GA. If necessary, begin dextrose infusion or increase dextrose concentration of IV fluids from 5 to 10% to prevent hypoglycemia. Adjust dextrose infusion and insulin dose (by subcutaneous injection of rapid-acting insulin for minor surgery) to maintain blood glucose in the range 5–10 mmol/L (90–180 mg/dL). For those receiving an IV insulin infusion, a single correction bolus of IV insulin (either using the child's usual correction factor or 5–10% of the child's usual total daily insulin dose, depending on the severity of hyperglycemia) may be given at the start of the infusion to correct hyperglycemia. Thereafter, correction of hyperglycemia should be based on adjustment of the rate of the IV insulin infusion (Table 1). If the blood glucose exceeds 14 mmol/L (~250 mg/dL), urine or blood ketones should also be measured. If there is an unexpected acute drop in blood pressure, NS (0.9% NaCl) or Ringer's lactate must be infused rapidly. In this case, potassium-containing fluids must *not* be infused rapidly.

Postoperative care

After surgery, start oral intake or continue IV dextrose infusion depending on the child's condition. Continue the IV insulin infusion or additional short-

or rapid-acting insulin as necessary until oral intake is resumed. Once the child is able to resume oral nutrition, resume the child's usual diabetes treatment regimen. Give short- or rapid-acting insulin (based on the child's usual insulin:carbohydrate ratio and correction factor), if needed, to reduce hyperglycemia or to match food intake.

Special circumstances

Emergency surgery

Although the majority of surgical procedures are elective, both minor and major surgical procedures may occur as emergencies. It is important to remember that diabetic ketoacidosis may present as an 'acute abdomen' and that acute illness may precipitate diabetic ketoacidosis. Before emergency surgery in a child with diabetes, always check blood glucose, blood BOHB (if available) or urinary ketone concentration, serum electrolytes, and blood gases if ketone or blood glucose levels are high. Do not give fluid, food, or medication by mouth because, in some emergency situations, the stomach must be emptied by a nasogastric tube. Always secure IV access and check weight before anesthesia. If ketoacidosis is present, follow an established treatment protocol for diabetic ketoacidosis and delay surgery, if possible, until circulating volume and electrolyte deficits are corrected and, ideally, until acidosis has resolved. If there is no ketoacidosis, start IV fluids and insulin management as for elective surgery.

Type 2 diabetes patients on oral medication alone

For patients with type 2 diabetes treated with insulin, follow the insulin guidelines as for elective surgery, depending on type of insulin regimen. For pediatric patients with type 2 diabetes on metformin, the timing of discontinuation will depend on the expected length of the procedure. Use of metformin has been associated with lactic acidosis, with risk that is increased by renal insufficiency (23). As lactic acidosis is both a rare and life threatening event, limited data are available to inform guidelines for perioperative management (24, 25). Therefore recommendations are that for major surgery (lasting at least 2 h) when conditions predisposing to additional risk factors, such as renal insufficiency or tissue hypoperfusion are most likely to be present, metformin should be discontinued 24 h before the procedure. Further, in the event of emergency surgery and <24 h since the last dose, it is essential to maintain hydration with IV fluids before, during, and after surgery. For minor surgery (i.e., less than 2 h), metformin may be discontinued on the day of the procedure. In all cases, metformin should be withheld for 48 h after surgery and until normal renal

function has been confirmed before restarting. For sulfonylureas, thiazolidinediones, DPP-4 inhibitors, and GLP-1 analogs, stop the medication on the day of surgery. Patients undergoing a major surgical procedure expected to last at least 2 h should be started on an IV insulin infusion as described above. For those undergoing minor procedures, monitor blood glucose hourly and if greater than 10 mmol/L (180 mg/dL), treat with subcutaneous rapid-acting insulin (0.1 unit/kg up to 10 units) no more frequently than every 3 h.

Conclusion

Whenever possible, surgery on children and adolescents with diabetes should be performed at centers with appropriate personnel and facilities to care for children with diabetes. To ensure the highest level of safety, careful liaison is required between surgical, anesthetic, and children's diabetes care teams before admission to the hospital for elective surgery and as soon as possible after admission for emergency surgery. Centers performing surgical procedures on children with diabetes should have written protocols for postoperative management of diabetes on the wards where children are admitted. Elective surgery should be scheduled as the first case on a surgical list, preferably in the morning. IV access, infusion of dextrose, and frequent blood glucose monitoring are essential whenever GA is given. Dextrose 5% is usually sufficient; dextrose 10% may be necessary when there is an increased risk of hypoglycemia. Elevated blood ketone and blood glucose concentrations require extra insulin and, possibly, additional IV fluid for correction. In these situations, consider whether it is appropriate to delay and reschedule an elective surgical procedure. A bedside meter that measures BOHB levels can be useful to guide management of these patients (26).

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Conflict of interest

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Psychological care of children and adolescents with type 1 diabetes

Delamater AM, de Wit M, McDarby V, Malik J, Acerini CL. Psychological care of children and adolescents with type 1 diabetes.

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1–3).

Executive summary and Recommendations

The following summary and recommendations build upon the previous ISPAD Guidelines (1) and are consistent with the latest statements and guidelines issued by the American Diabetes Association (2), Australia (APEG – Clinical Practice Guidelines, www.nhmrc.gov.au/publications/pdf/cp102.pdf), Canada (www.diabetes.ca/cpg2003), and the UK (www.nice.org.uk/pdf/type1diabetes).

- Young people with diabetes appear to have a greater incidence of depression, anxiety, psychological distress, and eating disorders compared to their healthy peers (A).
- Children and young people with chronic poor metabolic control, including recurrent diabetic ketoacidosis (DKA), are more likely to have underlying psychosocial problems or psychiatric disorders than children in good metabolic control (A, B).

- Resources should be made available to include professionals with expertise in the mental and behavioral health of children and adolescents within the interdisciplinary diabetes health care team. These mental health specialists should include psychologists, social workers, and psychiatrists (E).
- Mental health professionals should be available to interact not only with patients and families at clinic visits to conduct screening and more complete assessments of psychosocial functioning, but also to support the diabetes team in the recognition and management of mental health and behavior problems (A, E).
- There should be easy access to consulting psychiatrists for cases involving severe psychopathology and the potential need for psychotropic medications (E).
- All mental and behavioral health specialists should have training in diabetes and its management (E).
- The interdisciplinary diabetes health care team should maintain regular, consistent, and uninterrupted contact with patients and their families. When clinic visits are missed or not frequent, other modes

- of contact such as phone, SMS texting, or e-mail should be made available (B, E).
- Young people with diabetes are at increased risk for information processing weaknesses and learning problems, especially if there is a background of early diabetes onset, severe hypoglycemia, or chronic hyperglycemia (B).
 - Assessment of developmental progress in all domains of quality of life (i.e., physical, intellectual, academic, emotional, and social development) should be conducted on a routine basis (A, B, E).
 - Quality of life can be reliably measured with good clinical utility (A).
 - It is especially important to monitor the school performance of children who developed diabetes before age 5 yr, and with a history of significant hypoglycemic episodes and/or chronic hyperglycemia at early ages (B). These children, as well as all children experiencing learning difficulties at school, should be referred for a psycho-educational or neuropsychological evaluation in order to determine if learning disabilities are present (B).
 - Specific diabetes care plans should be formulated for the school setting and training conducted with school staff concerning diabetes management (B, E).
 - Routine assessment should be made of developmental adjustment to and understanding of diabetes management, including diabetes-related knowledge, insulin adjustment skills, goal setting, problem-solving abilities, regimen adherence, and self-care autonomy and competence. This is especially important during late childhood and prior to adolescence when in many families the child may take on diabetes management responsibilities without adequate maturity for effective self-care (B).
 - Identification of psychosocial adjustment problems, depression, eating disorders, and other psychiatric disorders should be performed at planned intervals and by appropriately trained mental health professionals (B, E). These assessments are particularly important in young people not achieving treatment goals or who exhibit chronically poor metabolic control (e.g., high HbA1c, recurrent DKA) (B, E).
 - Several family factors including levels of family cohesion, agreement about diabetes management responsibilities, and levels of supportive and collaborative problem-solving behaviors influence treatment regimen adherence and glycemic control (B, C). Family conflict is associated with lower regimen adherence and poor glycemic control (B, C).
 - The interdisciplinary team should assess general family functioning (conflict, cohesion, adaptability, and parental psychopathology) and diabetes-related functioning (communication, parental involvement and support, and roles and responsibilities for self-care behaviors) especially when there is evidence of cultural, language, or family problems or difficulties in adjustment to diabetes (A, B, E).
 - The interdisciplinary team should aim to provide preventive interventions for patients and families (including training parents in effective behavior management skills) at key developmental times, particularly after diagnosis and prior to adolescence (A, E). These interventions should emphasize appropriate family involvement and support (i.e., teamwork) in diabetes management, effective problem-solving and self-management skills, and realistic expectations about glycemic control (A, E).
 - Evidence-based psychosocial, behavioral, or psychiatric interventions should be made available for patients or families exhibiting conflict, disordered communication, behavioral or psychiatric difficulties, or adherence problems affecting glycemic control (A, B, E). Developmental needs of children and adolescents should be considered while planning interventions incorporating social, emotional, and tangible support (C, E).
 - In counseling young people and parents regarding advances in diabetes management, and encouraging the intensification of insulin regimens, motivational interviewing may be useful (A). This may help in clarifying patient and parental goals and resolve ambivalence about regimen intensification. Patients should not be denied access to regimen intensification based on perceptions of limited competence, as even youth with low self-management competence have been shown to improve with intensive insulin therapy (A).
 - Adolescents should assume increasing responsibility for diabetes management tasks but with continuing, mutually agreed parental involvement and support (A, E). The transition to adult diabetes care should be discussed, negotiated, and carefully planned with adolescents, their parents, and the adult diabetes team well in advance of the actual transfer to adult care (E) (see ISPAD Clinical Practice Consensus Guidelines on 'Diabetes in Adolescence' – Assessment and management of hypoglycemia in children and adolescents with diabetes).

Introduction

A substantial research base developed over the past 30 yr provides evidence for the significant role of psychosocial factors in the management of type

1 diabetes in children and adolescents (1–5). We review the main findings from studies of psychological adjustment, psychiatric disorders, neurocognitive and educational functioning, family dynamics, social support, stress and coping, quality of life, and behavioral interventions in children and adolescents with type 1 diabetes. Based on these research findings, recommendations for optimal psychological care are offered.

The ISPAD Consensus Guidelines 2000 stated that ‘Psychosocial factors are the most important influences affecting the care and management of diabetes’, and went on to make the following three general recommendations (6):

- (i) Social workers and psychologists should be part of the interdisciplinary health care team.
- (ii) Overt psychological problems in young persons or family members should receive support from the diabetes care team and expert attention from mental health professionals.
- (iii) The diabetes care team should receive training in the recognition, identification, and provision of information and counseling on psychosocial problems related to diabetes.

After reviewing the evidence base on psychological issues and interventions for children and adolescents with type 1 diabetes, these general recommendations remain appropriate and are developed further with more specific recommendations for psychological care.

Psychological adjustment and psychiatric disorders

Young people with diabetes appear to have a greater incidence of depression, anxiety, psychological distress, and eating disorders compared to their healthy peers (7, 8). Research findings indicate that children with type 1 diabetes are at risk for adjustment problems during the initial period of adaptation after diagnosis (9, 10). When adjustment problems exist, children are at higher risk for continued adjustment difficulties (10–13). In a 10-yr prospective study from the diagnosis of type 1 diabetes, adolescents were at high risk for various psychiatric diagnoses; females were more likely than males to receive a diagnosis, and half of those with a history of poor glycemic control had a psychiatric diagnosis (14). However, a recent longitudinal study from adolescence into emerging adulthood did not reveal group differences in psychosocial adjustment (15, 16). More recent studies suggest differences between children with and without diabetes appear to be smaller (7). Nevertheless, about 15% of youth with diabetes report elevated levels of psychological

distress, with potential negative consequences for self-care, and studies indicate that behavioral problems are associated with poor glycemic control (17, 18).

Studies indicate that depression and anxiety are related with less frequent glucose monitoring and poorer glycemic control (19, 20). Results from the SEARCH study in the USA found that 14% of youth with diabetes reported mild depression and 8.6% reported moderate to severe depression; girls reported more depressive symptoms than boys, and depression was associated with poorer glycemic control and increased diabetes-related hospitalizations (21). A recent meta-analysis showed that depression is associated with poorer treatment adherence, and this association is even stronger in more recent studies; the association between depression and glycemic control is small to moderate, and smaller in more recent studies (22). Prospective studies indicate that greater depressive symptoms predict less frequent blood glucose monitoring, poorer quality of life, and poorer glycemic control over time (23, 24). Children with recurrent DKA are more likely to have psychiatric disorders than children in good glycemic control (25). Poor glycemic control has also been associated with a number of other psychosocial problems including anxiety (20), poor self-esteem, and diabetes-distress (26–28). When psychological adjustment problems persist into late adolescence, there is evidence indicating greater risk for poor diabetes management during early adulthood (29, 30). However, more research in this area is needed.

Youth who are depressed are also at an increased risk for disordered eating behavior (31). There is evidence that adolescents with diabetes, especially girls, have a higher incidence of disturbed eating behavior and eating disorders (8). It is estimated that 7% of adolescent girls with type 1 diabetes may meet diagnostic criteria for an eating disorder, a rate twice as common as in girls without diabetes (8). Disordered eating behavior is more prevalent in adolescent girls with type 1 diabetes (40%) than their peers (33%) (31). Results of a recent meta-analysis indicated that eating disorders are associated with poor glycemic control (8), although a recent longitudinal study did not show this association (31). Even at subclinical levels, glycemic control has been observed to worsen with increasing symptoms of eating disorder (32–34). Without intervention, disordered eating and insulin manipulation may worsen over time and increase the risk of serious health complications (35–37)

Neurocognitive and school functioning

Studies of neurocognitive functioning indicate that young people with diabetes are at increased risk for information processing weaknesses and learning problems, especially with early diabetes onset (38–41),

history of severe hypoglycemia (40–42), and chronic hyperglycemia, even among very young children (43, 44). Research also indicates that diabetic youths are more likely to have learning problems, with such problems more frequent among boys than girls (45, 46). Academic achievement, school performance, and classroom attention are lower in children with poor metabolic control (47–49).

Prospective studies of newly diagnosed children have demonstrated mild neuropsychological deficits 2 yr after diagnosis, with reduced speed of information processing and decrements in conceptual reasoning and acquisition of new knowledge (14). Such problems were predicted by early onset of diabetes (prior to age 4 yr) and were related to poorer visuospatial functioning and both recurrent severe hypoglycemia and hyperglycemia, which was related to decreased memory and learning capacity (50). Study of neuropsychological functioning 12 yr after diagnosis found that children with diabetes performed more poorly on working memory than control children (51). Children with early onset diabetes (before age 4 yr) showed poorer sustained and divided attention and mental efficiency, while those with a history of recurrent severe hypoglycemia performed more poorly on measures of verbal ability, working memory, and non-verbal processing speed and those with chronic hyperglycemia showed poorer working memory (51). The results of meta-analytic studies indicate that children with type 1 diabetes have a variety of mild cognitive impairments and slightly reduced overall intellectual functioning (52, 53).

Parents report considerable anxiety when their children are in school, are not aware of federal laws to accommodate their children with diabetes, and believe that schools do not facilitate optimal treatment for their children while in school settings (54). In describing school experiences of students with diabetes, better glycemic control and quality of life occurs when school personnel and friends receive some training in diabetes and its management (55).

Family functioning

The research literature has consistently demonstrated that family factors are integral for the management of diabetes in children (1). The findings from a number of cross-sectional and prospective studies have shown that high levels of family cohesion, authoritative parenting, agreement about diabetes management responsibilities, supportive behaviors, and collaborative problem-solving are associated with better regimen adherence and glycemic control, while conflict, diffusion of responsibilities, and regimen-related conflict have been associated with worse regimen adherence and glycemic control (56–68). Family

conflict and negative affect related to blood glucose monitoring has also been associated with depression (19). Having a collaborative relationship between youth and their parents with shared responsibilities for diabetes management is associated not only with better regimen adherence, but also with improved emotional functioning (62, 69). Significant family dysfunction for the majority of families has been observed in clinical studies of adolescents with recurrent DKA (25, 64, 70, 71). Studies have also shown sociodemographic factors such as single-parenthood (72–74) and lower income and ethnic minority status (75–81) are associated with greater risk for poor control of diabetes.

It is important to note that many parents have psychological problems after the diagnosis of type 1 diabetes in their children. One recent review indicated that on average 33.5% of parents report distress at diagnosis, with 19% of parents reporting distress 1 to 4 yr after diagnosis (82). Mothers appear to be at risk for psychological adjustment problems after their child's diagnosis, with clinically significant depression noted in approximately one third of mothers; however, most of these adjustment problems are resolved within the first year after the child's diagnosis (83). Fewer studies have addressed psychological functioning in fathers. One study found that 24% of mothers and 22% of fathers met criteria for a diagnosis of post-traumatic stress disorder 6 wk after their child had been diagnosed (84). Another study found that psychological maladjustment of fathers predicted poor glycemic control in children 5 yr after diagnosis (85). Fear of hypoglycemia has also been found to be common in parents of children with diabetes (86) and is associated with emotional distress and poorer glycemic control in children (87).

Social support

Social support from parents and other family members is especially important for children and adolescents with type 1 diabetes. Research has shown that family members who provide high levels of support for diabetes care have youngsters who adhere better to their diabetes regimen (58). It was also noted that levels of diabetes-specific family support were inversely related to youngsters' age, with older children and adolescents reporting significantly less family support for diabetes. Youths may receive instrumental support from their families and also considerable emotional support from their friends (58, 88–91). When youth attribute negative peer reactions to their self-care, they are more likely to have adherence difficulties and increased diabetes stress, which in turn worsens glycemic control (92). Fear of stigmatization and sense of autonomy appeared to be major barriers withholding adolescents to solicit required support from peers (88). Poor peer

relations has been associated with decreased regimen adherence and worse glycemic control over time, while more family support predicted better glycemic control (93). Providing support to parents after the diagnosis of diabetes of their child is an important need and can promote better diabetes management (94, 95).

Stress and coping

Studies have shown that children with high life stress tend to have worse glycemic control (92, 96, 97). Daily stressors faced by younger children are usually related to friends/peers and siblings, and their coping behaviors include choosing an alternate activity and taking personal responsibility (98). Diabetes-specific stress has also been linked to poor glycemic control (28, 27). Research examining attributional and coping styles has indicated that youths in poor metabolic control are more likely to use the learned helplessness style (99) and engage in avoidance and wishful thinking in response to stress (100), while youths in good glycemic control have high levels of self-efficacy (101) and engage in active coping (102–106). A longitudinal study suggested a reciprocal relationship between active coping and better glycemic control, while avoidance coping was linked with worse glycemic control and increased psychological stress (103). Maladaptive coping has also been associated with poor regimen adherence (107). Resilience is associated with better diabetes management, quality of life, and glycemic control (104, 108).

Research addressing the health belief model in adolescents indicate that beliefs related to the seriousness of diabetes, personal vulnerability to complications, costs of regimen adherence, and beliefs in the efficacy of treatment have been associated with both regimen adherence and glycemic control (109–111). Studies have also shown that their personal models of illness belief for diabetes were associated with psychological adjustment and regimen adherence: greater impact of diabetes was related to increased anxiety, while beliefs about the effectiveness of treatment predicted better dietary self-care (112). Personal model beliefs about diabetes were also shown to mediate the relationship between personality variables (emotional stability and conscientiousness) and self-care behaviors (113). Studies of health risks associated with diabetes indicate that youth underestimate their own risks while acknowledging greater risks of diabetes attributed to other youths (114).

Identification and improvements in primary caregivers (mothers') coping may have the potential to improve both maternal and adolescent outcomes (115–119). Children with parental dyads exhibiting the negotiator coping pattern had better glycemic control than children with parents classified as avoiders or doers (120).

Quality of life

In general, children with diabetes rate their own quality of life as similar to their healthy peers (121). However, parents tend to rate their child's quality of life somewhat lower (122–124). Boys report better quality of life as well as youth with longer diabetes duration and those from a better socioeconomic background (121, 125–129). Lower quality of life seems associated with depression (130) and a negative family environment, especially diabetes conflicts (131). Less favorable quality of life also appears to be related with youths' perceptions that diabetes is upsetting, difficult to manage, and stressful, as well as fear of hypoglycemia (131, 132). There is some evidence that better quality of life is associated with better glycemic control, but the relationship between glycemic control and quality of life appears modest (124, 133–135). In a prospective study, poorer quality of life predicted subsequent poor glycemic control via less frequent blood glucose monitoring (136). Quality of life does not appear to be adversely affected by use of the insulin pump (127, 137, 138), and may be associated with improved quality of life (130). In addition, use of continuous glucose monitoring does not seem to adversely affect quality of life (139).

Psychosocial and behavioral interventions

Previous systematic reviews of the literature indicate that a number of controlled studies have shown the efficacy of psychosocial and behavioral interventions for children and adolescents with diabetes, although this literature is not without some methodological limitations (3, 4, 140–142). Most of these interventions have included the family as an integral part of treatment.

The results of these studies indicate that family-based, behavioral procedures such as goal-setting, self-monitoring, positive reinforcement, behavioral contracts, supportive parental communications, and appropriately shared responsibility for diabetes management have improved regimen adherence and glycemic control (141, 143). In addition, these interventions have improved the parent–adolescent relationship (141, 144–146), and improved regimen adherence (146). Studies of behavioral family systems therapy with diabetes-specific tailoring have shown improvements in family conflict and regimen adherence (147) as well as improved glycemic control over 18 months (148). Controlled research has demonstrated this approach to improve parent–adolescent communication and problem-solving which in turn was associated with improvements in glycemic control (149).

Given the crisis that diagnosis presents for children and families, the period just after diagnosis presents opportunities for intervention. Interdisciplinary intervention programs have been described and reported

to improve outcomes (150, 151). Psycho-educational interventions with children and their families that promote problem-solving skills and increase parental support early in the disease course have been shown to improve long-term glycemic control in children (152). Other trials involving psychosocial intervention after diagnosis showed improved family functioning without improved glycemic control (153, 154).

Research has shown that when parents allow older children and adolescents to have self-care autonomy without sufficient cognitive and social maturity, youths are more likely to have problems with diabetes management (155). Thus, a critical aspect of behavioral family management of diabetes is finding ways for parents and family members to remain involved and supportive, but not intrusive, in their children's daily care.

An intervention based on family-focused teamwork increased family involvement without causing family conflict or adversely affecting youth quality of life, and helped prevent worsening of glycemic control (156). A psycho-educational intervention delivered by a 'care ambassador' at regular outpatient visits was shown to improve the frequency of outpatient visits, and reduced acute adverse outcomes such as hypoglycemia and emergency department visits (157).

Another approach utilized intensive home-based multi-systemic therapy with inner city adolescents in chronically poor metabolic control, a patient population that has not received much attention in the intervention literature. Initial studies of this approach suggested that it had potential to improve outcomes (158). The results of a larger randomized trial indicated this approach improved frequency of blood glucose monitoring, reduced inpatient admissions, improved glycemic control, and reduced medical costs (159, 160). A more recent study demonstrated reduced hospitalizations and costs for this high-risk group of adolescent patients using multi-systemic therapy (161).

Peer group interventions have also been evaluated. Results indicate that peer group support and problem-solving can improve short-term glycemic control (162). Training in group coping skills improved glycemic control and quality of life for adolescents involved in intensive insulin regimens (163–165). Stress management, problem-solving, and coping skills training delivered in small groups of youths has reduced diabetes-related stress (166, 167), improved social interaction (168), and increased glucose monitoring and improved glycemic control (169).

It is important to maintain regular ongoing contact with families, as research findings indicate that children who have infrequent and irregular visits with the health care team are more likely to have glycemic control problems (170, 171). Research indicates that early adolescence represents a high risk time for diabetes management, with worsening of adherence

observed over time (172), which may be due to decreased parental involvement.

Motivational interviewing appears to be a promising approach for adolescents, with initial studies showing improved glycemic control (173, 174). A larger multi-center randomized trial demonstrated that motivational interviewing with adolescents improved long-term glycemic control and quality of life (175). Another study targeting motivation with an individualized personal trainer showed improved glycemic outcomes in older but not younger adolescents (176). More recently it was demonstrated that this approach had long-term positive effects on glycemic control in older adolescents (177).

Several recent studies have examined coping skills training with younger, school-aged children. Results indicate that this approach had some favorable effects on life satisfaction and family functioning (178). Although coping skills training for younger children was not shown to be more effective than an educational intervention, results from controlled studies do support the use of group interventions for children in this age range (179). Furthermore, coping skills training with parents of young children has also been shown to be helpful, although outcomes were not significantly different from the control group that received educational support (116).

More studies have recently been conducted on behavioral interventions integrated with outpatient medical clinic appointments. For example, monitoring and discussing quality of life issues with adolescent patients was found to improve psychosocial functioning over time (180). A family-centered program integrated with routine clinic appointments led to improvements in glycemic control and parental involvement when families participated in two or more such sessions over the course of a 12-month follow-up (181). In a large multi-site randomized trial, a family teamwork intervention delivered at the time of quarterly outpatient clinic visits led to improved glycemic control for young adolescents, but effects were not as strong as that for older children (182, 183).

Recent studies have examined the use of the Internet to deliver behavioral interventions. For example, it was demonstrated that using an Internet program for diabetes problem-solving led to significant improvements in diabetes management and problem-solving, with stable glycemic control (184). This approach was particularly sensitive to diabetes management barriers with regard to social issues, time pressures, and dealing with emotions (185). Another study examined the effects of coping skills training for adolescents delivered over the Internet, compared with an Internet-delivered educational intervention. The results of this randomized controlled multi-site trial indicated clinical improvements for youth in

both groups, supporting the concept that behavioral interventions can be effectively applied to youth with type 1 diabetes using the Internet (186).

A meta-analysis of intervention studies to promote regimen adherence in youth with type 1 diabetes was conducted and found 15 studies that met criteria for analysis (187). While the results indicated small effect sizes for improvements in glycemic control, multi-component interventions addressing psychosocial and emotional processes had stronger effects. In a review of family-centered interventions, nine studies were examined and found that such interventions improve glycemic control and family functioning while reducing family conflict (188).

In summary, the results of controlled intervention research have shown that family-based interventions utilizing positive reinforcement and behavioral contracts, communication, and problem-solving skills training, negotiation of diabetes management goals, and collaborative parental involvement have led not only to improved regimen behaviors and glycemic control, but also to improved family relationships. Group interventions for young people with diabetes targeting coping and stress management skills have also shown positive effects on regimen adherence, glycemic control, and quality of life. Individual interventions with adolescents have shown motivational interviewing to improve long-term glycemic control and psychosocial outcomes. There is growing evidence supporting the use of the Internet to deliver behavioral interventions.

Conflicts of interest

The authors have declared no conflicts of interest.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Diabetes in adolescence

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- Adolescence is the transitional phase of development between childhood and adulthood.
- Health care and emotional needs are distinctly different from younger children and older adults.
- It is important to understand the psychosocial and physiological development of adolescence and recognize that chronic diseases like diabetes have the potential to inhibit life experiences (E).
- Many adolescents experience a deterioration in metabolic control – attributable to the following:
 - endocrine changes leading to increased insulin resistance (B),
 - erratic meal and exercise patterns (C),
 - poor adherence to treatment regimens (C),
 - eating disorders (C), and
 - hazardous and risk-taking behaviors (C/E).
- Increase in weight gain, particularly in females may be observed (C/E) provoking insulin omission to effect weight loss (C).
- It is essential to develop appropriate communication skills to facilitate teaching and education, and recognize the need for privacy and confidentiality for this age group (E).

- To-date, psychoeducation interventions have demonstrated modest benefit on psychological outcomes, but no effect on glycemic control (B/C).
- Recent randomized controlled trials of motivational interviewing have shown no benefit in either psychological measures or glycemic control (A).
- Developing a trusting and motivating relationship between health care professionals and the adolescent patient and maintaining continuity may result in better patient self-care (C/D).
- Maintaining parental support and involvement throughout adolescence is associated with better outcomes (C/E).
- Identifying the need for specialized psychological counseling may be helpful and can be facilitated using specific screening tools (E).
- Providing health education opportunities utilizing strategies that optimize self-care behavior and that involve open-ended discussion, problem solving, negotiated target setting, and the use of modern technology are recommended (B/E).
- Education and advice on a variety of health care matters, including employment, driving, alcohol, drugs, sexual health, and contraception, should be provided taking into account background cultural and religious influences (E).

- There should be no discrimination or stigma against people with diabetes in the workplace (E).
- Organize regular screening for diabetes complications (E).
- Encourage understanding of the need for and immediate benefits of improved metabolic control (E).
- Recognize the signs of mental health problems (depression, eating disorders, illicit drug usage, etc.) and the occasional need for psychiatric treatment (E).
- Recognize that young people have differing views on the appropriate age of transfer of their care to young adult diabetes services (C/E).
- Planned coordinated transition to adult care should be provided at the most appropriate time (E).

Adolescence is the transitional phase of development between childhood and adulthood that incorporates the biological and psychosocial changes of puberty. It imposes unique challenges on the individual with diabetes, their family, and the diabetes care team (1, 2). Although the majority of adolescents adapt well to the difficult challenges of puberty, it must be recognized that their health care and emotional needs are distinctly different from those of younger children or older adults. Adolescence involves training to become an independent adult and may result in failures and mistakes as well as success.

In the context of type 1 diabetes many adolescents experience a deterioration in metabolic control (3–6) often attributable to erratic meal and exercise patterns (7, 8), poor adherence to treatment regimens (9–12), hazardous and risk-taking behaviors (1, 2, 13, 14), eating disorders (15–20) and endocrine changes associated with puberty, leading to greater insulin resistance (21).

Changes in body habitus, particularly weight gain in females (3, 5, 22–25) may be unwanted diabetes-related side effects, sometimes associated with changes in the tempo of pubertal maturation (25, 26) provoking insulin omission to effect weight loss (12, 16, 18).

It is therefore recommended (1, 2, 27–32) that those providing care for adolescents with diabetes should:

- Understand the psychosocial and physiological development of adolescence (1, 2). This includes the recognition of the need for young people to shift (around the age of 10 yr onwards) from ‘concrete thinking’, with limited abstract capacity for understanding time perspectives or consequences of their actions, into adult cognitive capacity with a more realistic perspective of the future, which is achieved at a variable rate toward late adolescence (33).
- Recognize that chronic conditions may inhibit some young people from exploring life, while others

deliberately explore risk-taking behavior involving their diabetes care.

- Develop communication skills [e.g., trusting, authoritative (not authoritarian), allowing adequate time, open questioning, patient-centered, observing non-verbal messages and confidentiality].
- Understand that attending to the developmental needs of young people may be just as important for quality of life as diabetes specific treatment (34, 35).
- Recognize the intensity of the changing social environment on behavior. Adolescents’ experience a strong need to fit in and be accepted outside the family – most importantly by peers.
- Acknowledge the emerging differences in lifestyle and changing needs of adolescents. Exploring various life styles is part of identity development and includes experimentation in many domains, most commonly in the company of peers.
- Identify the components of care unique to adolescents.
- Provide planned transition to adult care at the most appropriate time (35).

The weighted evidence base supporting these recommendations has been recently reviewed in both the Australian National Health and Medical Research Council guidelines (30) and UK National Institute of Clinical Excellence (NICE) guidelines (32).

Identifying the components of care that are unique to adolescents

Most aspects of optimal care of adolescents with diabetes have not been subjected to rigorous enquiry, hence results are conflicting. Extensive review of psychoeducational interventions has concluded that they may have modest benefit on psychological outcomes but not on glycemic control, although the methodological quality of most studies was moderate to poor (36, 37). Recent robustly designed randomized controlled trials of motivational interviewing interventions through training programs for pediatric diabetes teams appear to lead to no improvement in either psychosocial measures or hemoglobin A1c (HbA1c) levels (38).

Suggested care strategies might involve:

- Developing a trusting relationship between the adolescent and the diabetes care team, including through familiarity with staff and continuity in care (1, 32, 39). Adolescents report better self-care when health care professionals are motivating (1, 40).
- Helping the adolescent to clarify priorities and to set small achievable targets particularly where there is conflict between the needs of diabetes management and the adolescent’s social development and peer activities.

Table 1. Parenting styles according to L. Steinberg (49) and freely interpreted by K. Berg-Kelly 2007, personal communication

	Demanding Challenging	Not demanding Not challenging
Empathic with young person	Authoritative	Lenient Permissive
Non-empathic Cold	Authoritarian Rigid	Unconcerned Neglectful Indifferent

- Providing well directed education to help understand the physiological changes of puberty, their effect on insulin dose, difficulties of weight control, and dietary regulation.
- Organizing regular screening for early signs of complications to encourage a practical understanding of the options available and the immediate, long-term and individual benefits of improved metabolic control (35, 41).
- Recognizing the emerging maturity of the adolescent, encouraging self-reliance and self-efficacy thus not only allowing consultations to be increasingly directed toward the adolescent but also retaining the trust and support of parents (42).
- Helping the adolescent and parents to negotiate new levels of parental involvement in diabetes care tasks (35).

Emerging independence is best pursued gradually:

- Helping parents in their changing role from full responsibility toward a gradual transition to cooperative care with the adolescent. This role change needs to be slow and gradual as continued parental support and involvement in day to day care is a strong determinant of improved clinical outcomes. This is based on evidence that parental support and involvement throughout adolescence is associated with better outcomes (C, E) (1, 42–48).
- Identifying and advising on which parenting styles are more likely to be successful than others [see Table 1 and (49)].

The authoritative parent sets age-appropriate demands respecting the maturity level and developmental needs, carefully explaining reasons for prohibiting certain behaviors and agreeing on strategies for behavior together with the young person in a respectful dialogue. The authoritative parent, however, does not bargain about serious matters and has a clear goal of what is important in the long run. Authoritative parents do not need much support but need medical information.

The authoritarian, rigid parent gives orders, puts his/her own ambitions first and does not consider needs and feelings of the child. The rigid and demanding families may need support to develop more adequate parenting individually or in groups.

The lenient, permissive parents are highly empathetic who seem to care too much about their children, over-identify themselves with the needs of their children and hate hurting them by getting into conflicts over routines.

The unconcerned, neglectful, and indifferent parents may have severe mental problems keeping them from understanding and helping their children. Neglectful parents require a careful social work-up to explore the roots of dysfunction.

- Having an index of suspicion for signs of mental health problems such as depression, eating disorders, ‘diabetes burnout’, illicit drug use, mental slowness, attention deficit hyperactivity disorder (ADHD), and neglectful or abusive family situations. Identifying the need for, and effectiveness of, specialized psychological counseling in some situations (50). The HEADS technique (acronym for Home, Education, Activities during spare time, Drugs and Sexual activities) is helpful when screening for psychosocial problems that might interfere with self-management (51).
- Providing health education, utilizing strategies that promote optimal health care behavior (see ISPAD Guideline Chapters on Psychological Issues and Education). Although there is consistent evidence that knowledge *per se* is predictive of better self-care and control this association is weak in adolescence (1). Thus, while it is essential that adolescents are provided with information about diabetes and its care, providing this information by conventional education alone may be insufficient to lead them to adopt optimal health care.
- Encouraging the adolescent to participate with parents and health care team members in making decisions about diabetes management.
- Enabling the adolescent to learn from mistakes without moral judgment.
- Offering a variety of educational opportunities including open-ended adolescent-orientated discussion and negotiation (52), discussing health-related quality of life issues (53), problem solving, target setting (50, 54), age-appropriate written materials, CDs/videos, text messaging (55), the use of the internet, social media, peer involvement, and group learning.
- Facilitated meetings with peers who have diabetes in order to receive advice, reflect and share experiences, and reduce feelings of isolation (56).

Sub-optimal metabolic control

The Diabetes Control and Complications Trial (DCCT) has unequivocally shown that intensive insulin therapy reduces risk of long-term vascular

complications, largely through improved HbA1c levels, and that better metabolic control in the early years of diabetes is also important in reducing this risk (57, 58). Metabolic control commonly deteriorates during adolescence, and this is partly due to physiological influences. However, the health care team should also consider the following:

- Socializing with peers is of utmost importance to most adolescents which often conflicts with their capacity to manage diabetes optimally.
- Adolescents with diabetes have the same needs for exploration as other young people but studies have shown that many of them are more vulnerable and subjected to more pressures to conform to peer norms (34, 35).
- Studies demonstrate slightly more involvement in health hazardous behavior in those with chronic conditions (14, 59).
- Adolescents may adopt non-demanding low risk metabolic control by deliberately adjusting their diabetes to a blood glucose level where they do not risk hypoglycemia or hyperglycemia/ketonemia and thus do not have their everyday life disturbed by diabetes.
- Some adolescents, particularly female, may manipulate insulin doses or dietary habits in order to reduce weight gain, which has the inevitable consequence of worse metabolic control and increased vascular complications risk (13).
- It may be helpful to negotiate from a cost-benefit stand-point to assist the young person to understand the short- and long-term costs of certain behaviors as well as the potential benefits.

Severe hypoglycemia

Severe hypoglycemia may be experienced during adolescence due to poor metabolic control, exacerbated by irregularities of lifestyle and risk-taking behaviour. In addition to the immediate effects on neurocognitive function, evidence shows an important link between severe hypoglycemia and preclinical atherosclerosis and acute and chronic cardiovascular events in later life (60, 61). This is relevant in the context of intensive insulin therapy that may increase the risk of severe hypoglycemia (62), although there is reassuring new evidence that hypoglycemia may be reduced in frequency by contemporary therapies (63) and careful attention to detailed education (64–66).

Specific concerns during adolescence include:

- Development of hypoglycemic unawareness or altered prodromal symptoms. An episode of severe hypoglycemia may lead to a period of altered awareness.

- Fears about hypoglycemia may be associated with poorer metabolic control (67).
- Confusion with alcohol intoxication.
- Confusion with illicit drug effects.
- Nocturnal or early morning episodes due to altered sleep patterns.
- The effect of hypoglycemia on driving.
- The effect of hypoglycemia on academic, sports, or work performance.

Young people should be encouraged to understand the benefits to them of better metabolic control. Advice should be given about hypoglycemia to enable adolescents to take positive measures in recognizing, managing, and preventing hypoglycemia (66, 68). Adolescents should be encouraged to inform friends about the risks, symptoms, and treatment of hypoglycemia during the altered routine of social engagements (1).

Alcohol, smoking, and drugs

Alcohol, tobacco, and illicit drug use is a serious concern in some communities during high school years (69). Notwithstanding the paucity of evidence of the variable contexts and type of alcohol consumption in adolescents with diabetes (70), advice on alcohol, smoking, and drugs should include:

- Encouragement to refrain from smoking and binge drinking, and advice on avoiding the dangers of drugs that may affect brain function or lead to dependence or addiction.
- Adopting a realistic advisory approach to alcohol rather than an absolute ban on medical grounds.
- Information on the effects of alcohol, particularly in young adolescents, on the liver by inhibiting gluconeogenesis with the possibility of either delayed severe hypoglycemia. This can variably combine with the carbohydrate content of the beverage to result in an unpredictable glycemic response (71).
- Methods of avoiding nocturnal hypoglycemia after drinking alcohol in the evening by ingesting carbohydrate while drinking, maintenance of good hydration, measuring blood glucose levels before bedtime, and having carbohydrate before sleep to minimize the risk of hypoglycemia.
- Ensuring that adolescents and their friends at parties and events where alcohol is consumed, are aware that hypoglycemia may occur when drinking alcohol without eating; that vomiting, particularly with omission of usual insulin, is dangerous and may be inhaled or lead to ketoacidosis; that hypoglycemia might be confused with intoxication and that it is important to check blood glucose levels before sleep.

Providing information for and education of colleagues or friends is increasingly important as the young person develops independence from the family, especially when living away from home at work, college, or university.

- Authoritative, but empathic, advice about smoking as an additional risk for the vascular complications of diabetes (C) (72, 73).
- Helping the adolescent who does smoke to stop by providing specific interventions that help with smoking cessation (nicotine-patch, cognitive-behavioral therapy, prescription drugs, etc.).
- Recognition that cannabis may alter eating habits (excess snacking during and loss of appetite after cannabis smoking) and may reduce motivation to maintain good metabolic control.
- Illicit drugs may alter brain function, increasing the risks of mistakes and mishaps with diabetes management.
- Acknowledgment that a risk reduction policy may be more realistic than an absolute ban on illicit drug experimentation.
- Introduce strategies for managing stress during adolescence other than medication, e.g., relaxation-training, exercise, psychological evaluation for anxiety or depression, hypnosis, etc.

Health care professionals should understand that educational messages which are motivating, problem solving, target setting, and which encourage adolescents toward developing their own strategies to avoid these problems are more successful than threats or inducing fear (E) (1, 35).

Driving

Hypoglycemia is the main factor which increases driving risk in people with diabetes (74), however, this risk is mitigated in an individual with glycemic awareness, stable metabolic control, and no visual disability to the extent where they are able to drive non-commercial vehicles (E) (75). Regulations vary in different countries. Studies have variably shown increased rates of driving accidents in drivers with type 1 diabetes (T1D) (75–77). Studies have also shown reductions in automobile accidents following specific hypoglycemia awareness training programs (C) (66–68).

The young person who plans to obtain a driving licence should be advised on the appropriate regulations and in particular:

- Prevention of hypoglycemia while driving (particularly if hypoglycemic unawareness is a problem) by blood glucose monitoring before starting to drive and appropriate food intake (75).

- Encouraging stable metabolic control (particularly avoidance of hypoglycemia) which may help determine whether a person with diabetes is eligible to hold a driving licence. Severe hypoglycemia in the preceding months causes many authorities to delay granting a licence.
- Regular visual acuity checks.

Employment

There should be no discrimination or stigma against people with diabetes in the workplace (77, 78). Most young people with diabetes should make good employees because of their ability to organize their lives and health care.

Advice on employment should include:

- Not concealing diabetes if asked about health and encouraging young people to inform potential employers about diabetes and how it is managed.
- The value of a good medical report from the diabetes care team may reassure employers that diabetes should not be a disadvantage in employment.
- Advice on those careers which may be unavailable to persons with diabetes, e.g., police, fire, armed and certain public services, driving large goods vehicles, or piloting airplanes. New technological developments may change these restrictions.
- Legal regulations vary between countries.

Reassurances to employers that young people with diabetes make excellent employees if they have shown mature self-care, self-discipline, and responsibility.

- Recommendations conclude that young people with diabetes should be prepared for the work place in the following ways:
 - Be responsible for self care including monitoring of blood glucose levels.
 - Be careful to avoid significant hypoglycemia.
 - Be candid about their diabetes to their employer.
 - Have a physician report to potential employers that supports the responsible diabetic young person.

Sexual health

Advice to young people with regards to sexual health will vary between different countries and cultures but would usually include (79):

- A non-judgmental approach to sexual activity.
- Advice where applicable on methods of avoiding pregnancy and sexually transmitted infections (STIs) for male as well as female adolescents.

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- Prevention of hypoglycemia during or after intercourse.
- Advice on genital hygiene, vulvovaginal candidiasis, menstrual disorders, and STIs.
- Pre-pregnancy counseling

Adolescent girls with diabetes should be aware of the importance of a planned pregnancy. Poor glycemic control around the time of conception increases the risks of congenital malformations, spontaneous abortion, and fetal death (C) (79–84). Pre-pregnancy counseling and education well in advance of the possibility of pregnancy is advisable with emphasis on:

- Ovulation is preserved, even when poor metabolic control and menstrual irregularities are present (85–87).
- The importance of good glycemic control before pregnancy, particularly the risks to the developing embryo and fetus.
- Understanding the importance of good control throughout pregnancy to avoid fetal macrosomia and neonatal hypoglycemia and also the avoidance of maternal hypoglycemia and ketoacidosis.
- Discussion with the young person and partner regarding the genetic risks of diabetes to their offspring.

Access to expert pregnancy management should include:

- Cooperative management by an obstetrician and physician with special experience in diabetes and pregnancy.
- Delivery of the baby in a hospital able to provide expert maternal, fetal, perinatal and neonatal care.
- Impotence

Males with long-standing diabetes may become impotent because of autonomic neuropathy (C) (88). Younger males may fear this complication and require expert counseling. Impotence in adolescence is rare and may be due to psychological reasons rather than diabetes itself.

Contraception

The diabetes care team should be sensitive to the religious and cultural influences affecting an individual's choice of contraceptive method (79).

- When a female with diabetes becomes sexually active she should do so with knowledge of how to avoid an unplanned pregnancy and STIs (E) (11, 12).

A planned pregnancy in a person with diabetes in excellent metabolic control and in good health carries

risks that are slightly higher than those in the general population, but not as elevated as previously reported (C) (89–91).

Barrier methods.

- Worldwide safe sex, STIs and HIV campaigns have made adolescents more aware of barrier methods, particularly condoms.
- Condoms offer the greatest protection against STDs to the whole genital tract (less against herpes), and substantial protection against pregnancy.
- Diaphragms are not recommended for the adolescent. Diaphragms are less effective contraception than the condom and do not protect against vaginal infection.
- Spermicidal gels probably increase the effectiveness of barrier methods.
- *Coitus interruptus*, a common practice among teenagers, is not recommended because it is associated with a high pregnancy rate.

Hormonal contraception and oral contraceptives.

- In the past, oral contraceptives (OCs) with 50 µg of ethinyl estradiol (EE) were thought to have an adverse effect on metabolic control and lipid profiles and increase the risks of hypertension, cardiovascular, and thromboembolic diseases (C) (79, 92, 93). Nowadays, OCs with 50 µg EE are rarely used.
- Newer OCs with a lower estrogen dose (≤ 35 µg or less EE) and newer progestogens have not been demonstrated to be associated with detrimental effects on metabolic control, weight, or lipid profile (C) (79, 93–97).
- Young people with diabetes on OCs should be monitored regularly, particularly blood pressure, side effects such as headaches, mood changes, breast changes, and genital infections.
- Patients without micro- or macro-vascular complications and diabetes duration < 20 yr may use any hormonal method (E) (98, 99).
- Patients with diabetes duration > 20 yr, or having micro- or macro-vascular complications should avoid using OCs, but may use progestin only methods, intrauterine device (IUD), or barrier methods (E) (98, 99).
- Diabetes *per se* is not a risk factor of venous thromboembolism (C) (100).
- All women taking OCs, including patients with diabetes, should be educated on the signs of thromboembolic diseases. Educate about clinical signs of alert using the acronyms ACHES (abdominal pain, chest pain, headaches, eye, and severe leg pain).

- Women with personal history of thrombotic disease should not use combined hormonal contraception (B) (98–101).
- If acne or hirsutism are a problem, the use of an OC containing an anti-androgenic progestins may be helpful (C) (102–104).
- Progesterone-only OCs may provide insufficient contraception for teenagers who are likely to forget the OCs.
- Similar to other adolescents without diabetes, in some circumstances if there is the possibility of an unwanted pregnancy it may be beneficial to advise sexually active young people about the availability of the ‘morning after’ hormone pill. No special considerations for the adolescent with diabetes are recommended in this setting (E) (105).
- Very obese patients should be aware of a decrease of contraceptive efficacy of hormonal contraception and higher risk of venous thromboembolism (C) (106).

Depot hormone injections.

- Medroxyprogesterone injections have been associated with decreased bone mass gain, which may be especially detrimental for the adolescent with T1D (E).
- No studies have evaluated combined hormonal monthly injection in patients with T1D, however, this method may be of useful when the individual has an erratic life style and is at high risk of pregnancy (E).

Long acting reversible contraceptions.

- Recently, long acting reversible contraceptions (LARCs), which include IUDs and the implantable rod, have been accepted as a first line contraceptive choice for nulliparous girls (E) (107, 108).
- IUDs provide no protection against STIs, but are not associated with more episodes of STIs.

Study and examinations

Most adolescents will engage in a level of secondary and/or tertiary education that will require some form of formal assessment such as examinations. These may be significant life events in that they will to varying extent determine further educational and vocational opportunities. Advice as to how a student may deal with their diabetes to optimize academic performance is frequently sought. Many students are well aware of the cognitive effects of hypoglycemia (109, 110) and thus may choose to run their glucose levels higher than usual during exam times. They should however be

counseled as to the equally negative cognitive impacts of hyperglycemia (111, 112). Glycemic responses to exams may vary with individual students stress responses, the type and length of the exam, and the time of day. Consequently students should undertake practice examinations in conditions that are as near as possible to those that will be experienced in the actual examination (i.e., same exam duration time, same time of the day, etc). Blood glucose levels should be checked immediately prior to and midway if a long exam (such as 3 h). Adjustments to insulin regimens and/or diet can then be made accordingly so as to maintain euglycemia during the exam. As a general principle over the course of the academic year, exercise should be encouraged to reduce stress, improve physical fitness, improve sleep patterns, and improve cognitive performance (113).

Transition from pediatric to adult services

The concept of transition implies a ‘planned, purposeful movement of the adolescent or young adult with a chronic disease from a child (and family) centered to an adult orientated health care system’ (2). The transition from a pediatric to an adult orientated service should not involve a sudden unanticipated transfer but an organized process of preparation and adaptation. The process should be a component of a high quality, multi-disciplinary diabetes service (including the use of linked databases) and must involve both teams of carers, an understanding of the two different systems of care and the differing expectations of those providing and those receiving care.

The appropriate age for transfer from a pediatric or adolescent service to adult care varies according to the maturity of the adolescent, the availability of appropriate services for the young person in an adult clinic and may be determined by hospital and clinic facilities and regulations. Young people have differing views on the appropriate age of transfer (32–35, 114, 115). Recent developmental psychology theory suggests that the transition should be toward emerging adulthood and not to young adult status (116). There is a potential danger that young people become lost in the transition process and cease regular attendance at the specialized service (C) (117). This is likely to be associated with poor adherence to treatment with increased risk of acute (12) and long-term complications of diabetes including increased mortality (C) (118). As no controlled studies have been performed the following recommendations are nearly all based on expert consensus opinion (E) (119).

For successful transition to an adult service, the following steps should be considered:

- Identifying an adult service able to provide for the needs of young adults with diabetes.

- Providing a joint adolescent or young adult clinic with members of both professional teams working together to facilitate the transition process for both adolescents and their parents.
- Liaison between the pediatric and adult services. Ideally this should involve identifying a specific person in the service (a 'key worker') who is able to move between both services to help the transition of the young person into the adult service. There is evidence that the appointment of a specialist nurse for adolescence has been successful in this role (C) (120). If such a person is not available, one of the pediatric staff should take responsibility for liaison with the adult service and both groups must have understanding of the services involved.
- Discussion with the adolescent and parent well in advance as to the best time for transfer, based on not only their own preference and readiness, but also on the availability of services and, in some countries, health care insurance requirements. It is preferable to have flexibility about age of transition as family circumstances and an adolescent's psychosocial maturity differ widely.
- Development of clear, documented plans for transition services, and provision of a clinical summary of the young person's medical history including indices of control, the results of complication screening and information on any comorbidities that may impact on how the person is managed medically.
- Good communication, including a written patient care pathway and protocol (30–32, 35), to facilitate understanding between all services providing care for the young person, particularly all members of the two diabetes teams and including, where available, primary care physicians and community nursing staff.
- Ensuring that there is no significant gap in care between leaving the pediatric service and entering the adult service and that the young person is not lost to follow-up care (35). This may occur if the young person fails to make or keep an appointment, or feels uncomfortable in the new service and loses touch with a specific named team member.
- The diabetes transition service should have mechanisms in place, including a database and a named professional, to identify and locate all young people who fail to attend follow-up consultations.

The adult service should be strongly encouraged to ensure long-term follow-up and outcome measurements of those who have developed diabetes as children and adolescents as many studies show poor glycemic control and longer term morbidities (C) (121, 122).

To date there have been very few robust studies investigating best models of transition to adult care

services (123). Several trials are currently underway attempting to address this lack of evidence base (124).

Conflicts of interest

The authors have declared no conflicts of interest.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Microvascular and macrovascular complications in children and adolescents

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1–3).

Executive summary and Recommendations

Prevention

- Intensive education and treatment should be used in children and adolescents to prevent or delay the onset and progression of complications (A).
- Improvement in glycemic control will reduce the risk for onset and progression of diabetes vascular complications (A).

Screening

- Screening for retinopathy and microalbuminuria should start from 10 yr of age, or at onset of puberty if this is earlier, with 2–5 yr diabetes duration (C) (Table 1).

Retinopathy

- Assessment for retinopathy should be performed by an ophthalmologist or a trained experienced observer through dilated pupils (B).
- Initial eye examination should also be considered to detect cataracts or major refractive errors (E).
- The frequency of retinopathy screening in general should occur annually, but should be more frequently if there are high risk features for visual loss. For those with duration <10 yr, minimal background retinopathy on fundus photography and reasonable glycemic control, biennial assessment by fundal photography can occur (E) (Table 1).
- Because of potential worsening of retinopathy for patients with longstanding poor glycemic control when control is improved, ophthalmological monitoring is recommended before initiation of

intensive treatment and at 3-month intervals for 6–12 months thereafter, particularly if retinopathy severity is at the moderate non-proliferative stage or worse at the time of intensification (E).

- Laser treatment reduces the rate of visual loss for individuals with vision-threatening retinopathy (severe proliferative retinopathy or proliferative retinopathy) (A).

Microalbuminuria

- Annual screening for albuminuria should be undertaken by any of these methods: first morning urine samples for urinary albumin/creatinine ratio (ACR) or timed urine collections for albumin excretion rates (AER) (E) (Table 1).
- Because of biological variability, two of three consecutive collections should be used as evidence of microalbuminuria. Confounders are exercise, menstrual bleeding, infections, fever, kidney diseases, and marked hyperglycemia. Abnormal screening tests should be repeated, as microalbuminuria may disappear and not be persistent (E).
- Angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB) agents should be used in patients with persistent microalbuminuria to prevent progression to proteinuria (E) (in adolescents).

Blood pressure

- Blood pressure (BP) should be measured at least annually (E). Hypertension is defined as average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) that is >95th percentile for gender, age, and height on more than three occasions (B).

- The blood pressure target for adolescents is <130/80 mmHg
- Confirmation of hypertension may be assisted by 24 h ambulatory blood pressure measurements (E).
- ACEI are recommended for use in children with diabetes and hypertension (E) Table 3. They have been effective and safe in children in short-term studies (A, B), but are not safe during pregnancy.

Lipids

- Screening for dyslipidemia should be performed soon after diagnosis (when diabetes stabilized) in all children with type 1 diabetes aged >10 yr (E). If normal results are obtained, this should be repeated every 5 yr (Table 1). If there is a family history of hypercholesterolemia, early cardiovascular disease (CVD) or if the family history is unknown, screening should commence as early as 2 yr of age (E).
- High low-density lipoprotein (LDL) cholesterol is defined as ≥ 2.6 mmol/L (100 mg/dL) (E). If this is present then interventions to improve metabolic control, dietary changes, and increased exercise should be instituted (Table 3).
- If the above interventions do not lower LDL cholesterol <4.1 mmol/L (or <3.4 mmol/L (130 mg/dL) and one or more CVD risk factors), statins should be considered in children aged >10 yr, although long-term safety is not established (E) (Table 3).

Lifestyle

- Cessation of smoking/never initiating smoking will reduce progression of microalbuminuria and CVD (B).

Table 1. Screening, risk factors and interventions for vascular complications

	When to commence screening?	Screening methods	Risk factors	Potential interventions
Retinopathy	Annually from age 10 or at onset of puberty if this is earlier, after 2 to 5 years' diabetes duration	Fundal photography or mydriatic ophthalmoscopy (less sensitive)	Hyperglycemia High blood pressure Lipid abnormalities Higher BMI	Improved glycemic control Laser therapy
Nephropathy	Annually from age 10 or at onset of puberty if this is earlier, after 2 to 5 years' diabetes duration	Urinary albumin/creatinine ratio or first morning albumin concentration	High blood pressure Lipid abnormalities Smoking	Improved glycemic control ACEI or ARBs Blood pressure lowering
Neuropathy	Unclear	History and physical examination	Hyperglycemia Higher BMI	Improved glycemic control
Macrovascular disease	After age 10 yr	Lipid profile every 5 yr, blood pressure annually	Hyperglycemia High blood pressure Lipid abnormalities Higher BMI Smoking	Improved glycemic control BP control Statins

ACEI, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure.

Macrovascular

- Screening of blood pressure and lipids is recommended, as above. The benefit of routine screening for other markers of macrovascular complications outside the research setting is unclear (E).

Type 2 diabetes

- Complications screening should commence at diagnosis. Attention to risk factors should be escalated because of the increased risk of complications and mortality (B).

Introduction

The long-term vascular complications of diabetes include retinopathy, nephropathy, neuropathy, and macrovascular disease. The outcomes are:

- visual impairment and blindness due to diabetic retinopathy;
- renal failure and hypertension due to diabetic nephropathy;
- pain, paresthesia, muscle weakness, and autonomic dysfunction due to diabetic neuropathy; and
- cardiac disease, peripheral vascular disease, and stroke due to macrovascular disease.

Clinically evident diabetes-related vascular complications are rare in childhood and adolescence. However, early functional and structural abnormalities may be present a few years after the onset of the disease.

Childhood and adolescence is a period during which intensive education and treatment may prevent or delay the onset and progression of complications in later adult life (1).

There has been a declining incidence of complications in young people, including retinopathy and nephropathy, reported in many areas with specialized clinics (2–6). In adults, the incidence and prevalence of retinopathy has declined over time (7–8). These changes have occurred over a period of time during which there have been major changes in diabetes management, identification of putative risk factors, and the advent of regular screening for complications (9, 10). However, there is no evidence that this is a worldwide occurrence: in areas where health care is not optimal, a greater risk of complications will remain (11, 12).

Interventional studies of intensive glycemic control

The Diabetes Control and Complications Trial (DCCT) was a multicenter, randomized controlled

clinical trial involving 1441 patients with type 1 diabetes conducted in North America from 1983 to 1993 (13). Patients were randomized to two treatment arms of intensive and conventional treatment which achieved a significantly lower hemoglobin A1c (HbA1c) in the intensive group. There were 195 pubertal adolescents (aged 13–17 yr) but no younger children (1). After completion of the DCCT (a median in the adolescent group of 7.4 yr) and hence the end of randomization, the Epidemiology of Diabetes Interventions and Complications (EDIC) study continued to follow patients. After 4 yr there was no significant difference in HbA1c between the former intensive and conventional treatment groups.

The DCCT provided unequivocal evidence that intensive diabetes treatment and improved glycemic control conferred a significant risk reduction for microvascular complications compared with conventional treatment (13).

The EDIC study demonstrated that this positive effect continued after randomization, i.e., that there was a memory effect of improved glycemic control. In addition it showed a positive effect of intensive therapy for reduction in macrovascular disease (14).

In the adolescent cohort, intensive treatment compared with conventional treatment, reduced the risk and progression of non-proliferative retinopathy by 53%, clinical neuropathy by 60%, and microalbuminuria by 54%. The difference in HbA1c was 8.1 vs. 9.8%. The benefits of intensive therapy persisted in the former adolescent cohort during the first four years of the EDIC study: the previously intensively managed group had 74% less retinopathy, 48% less microalbuminuria, and 85% less albuminuria (15).

Compared with conventional treatment, intensive treatment in the total age group reduced the risk of clinical neuropathy by 60%. Cardiovascular events were reduced by 50% in the previously intensively treated group compared with the control group during a mean 17 yr follow-up (14).

The DCCT confirmed that improved glycemic control may initially worsen diabetic retinopathy. However, within 1.5–3 yr, the advantage of intensive treatment is evident (16). In the DCCT, the long-term benefits of intensive insulin treatment outweighed the risk of early retinal deterioration, while in the EDIC study, the benefit of intensive treatment for retinopathy progression was sustained in adults for 10 years, but not in adolescents (17). This supports the need for long-term maintenance of glycemic targets.

Other risk factors for the development of complications

Longer duration of diabetes, older age, and puberty are risk factors for complications (18). The prepubertal

years of diabetes duration have a significantly lesser impact especially further from the onset of gonadarche (19); however, the risk of vascular complications is greater for those living with diabetes during puberty, compared with young people who develop diabetes after puberty (20). For the same diabetes duration, age and puberty increase the risk for retinopathy and elevated AER (6, 19–21). Longitudinal studies have also reported that younger age of type 1 diabetes onset, particularly before puberty, is associated with a longer time free of complications such as nephropathy and retinopathy (19). However, in the long-term this initial advantage disappears (22, 23).

High rates of cardiovascular risk factors have been found in children and adolescents with type 1 diabetes from Norway and in SEARCH for Diabetes in Youth (www.searchfordiabetes.org) SEARCH, a population based study from the USA (24, 25).

Smoking is associated with an increased risk of developing persistent microalbuminuria or macroalbuminuria (4, 26). The evidence for the effect of smoking on retinopathy is less clear (27), although changes in retinal microvasculature that are early markers of retinopathy (eg vessel diameter) have been associated with smoking (28). Type 1 diabetes and smoking interact to produce excess cardiovascular morbidity and mortality (29).

High BP and alterations in the circadian BP rhythm have been associated with the risk of developing nephropathy and retinopathy in youth with type 1 diabetes (30–32). Hypertension has a greater impact on CVD in diabetic patients than in non-diabetic individuals (33). BP control (<130/80 mmHg in adults) is effective in decreasing cardiovascular morbidity and mortality in diabetes (34).

Dyslipoproteinemia is associated with microalbuminuria and retinopathy development in the DCCT/EDIC (35, 36). This included higher total and LDL cholesterol and higher triglyceride levels for microalbuminuria, as well as larger LDL particle size and apolipoprotein B (apoB) in men.

Family history of complications increases the risk for nephropathy (37) and retinopathy (38). Higher body mass index (BMI) is a risk factor for retinopathy (39), neuropathy (40), microalbuminuria (41), and CVD (42, 43).

Life style issues also contribute to complications risk; sedentary men with diabetes have higher mortality than active individuals (44).

Diabetic retinopathy

Adolescents have a higher risk of progression to vision-threatening retinopathy (severe non-proliferative retinopathy or proliferative retinopathy) compared

with adults with diabetes (23, 45, 46). The progression may be rapid, especially in those with poor glycemic control (47). Hence, adolescence is the time when efforts should be directed to screening for early signs of diabetic retinopathy and modifiable risk factors. Regression of retinopathy can also occur (45, 46, 48, 49). After 20-yr diabetes duration the later onset group of type 1 patients aged <30 yr at diagnosis had less proliferative retinopathy (PDR) than the earlier onset group: 18 vs. 43%; examined 2007–2011, earlier group examined 1980–1996.

Progression of retinopathy

Non-proliferative (background) retinopathy is characterized by microaneurysms, retinal haemorrhages (blot, dot and flame-shaped), hard exudates (protein and lipid leakage), cotton wool spots (microinfarction), intraretinal microvascular abnormalities and beading, dilatation, constriction and tortuosity of vessels. Non-proliferative retinopathy can be classified as mild (microaneurysms only), moderate (more than microaneurysms) and severe (≥ 20 or more retinal hemorrhages in each of 4 quadrants, definite venous beading in 2 quadrants and intraretinal microvascular abnormalities in 1 quadrant).

Severe non-proliferative retinopathy is characterized by increasing vascular obstruction, progressive intraretinal microvascular abnormalities, and progressive ischemia with infarctions of the retinal nerve fibers causing cotton wool spots.

Mild and moderate non-proliferative retinopathy are not vision-threatening and do not invariably progress to proliferative retinopathy.

PDR is characterized by neovascularisation in the retina and/or vitreous posterior surface. The vessels may rupture or bleed into the vitreoretinal space which is vision-threatening. Advanced PDR can result in fibrosis and adhesions, which can cause hemorrhage and retinal detachment. High-risk characteristics for visual loss are the location and extent of neovascularisation and signs of vitreous or preretinal hemorrhage (50).

Diabetic macular edema (DME or maculopathy) is classified separately from stage of retinopathy, and is characterized by decreased vascular competence and microaneurysm formation which produce increased exudation and swelling in the central retina. DME is vision-threatening but is very uncommon in children and adolescents with type 1 diabetes.

Assessment of retinopathy

The most sensitive detection methods for retinopathy screening are bimicroscopic fundus slit examination through dilated pupils by an ophthalmologist or

optometrist and mydriatic seven-field stereoscopic retinal photography (51–54). The latter is optimal for research but not often available in the clinical setting. Other methods are mydriatic and non-mydriatic two-field fundal photography, direct ophthalmoscopy, indirect ophthalmoscopy, fundus fluorescein angiography, and optical coherence tomography (OCT). Fundal photography provides a validated result that can be useful for monitoring clinical quality and in research, but photographs may not be gradable in which case ophthalmoscopy needs to be performed; mydriasis can reduce the technical failure rate (55). Fluorescein angiography reveals functional abnormalities (vascular permeability) as well as structural abnormalities in the blood vessels whereas OCT reveals only structural abnormalities, specifically macular oedema.

The landmark study of retinopathy carried out in Wisconsin starting in 1980–1982, examined prevalence of retinopathy using seven-field stereoscopic retinal photography in people diagnosed with diabetes <30 yr of age and on insulin within 1 yr of diagnosis (48). With longer diabetes duration there was an increase in retinopathy, so that after 15 yr 98% had background retinopathy and after 35 yr duration 62% had PDR. This study helped establish the existence of screening for diabetic retinopathy and the search and treatment of risk factors. Subsequent changes in diabetes management have been associated with a reduction in PDR demonstrated by comparison with a later diagnosed study group. After 20 yr diabetes duration the later onset group of type 1 patients examined in 2007–2011, had less PDR than the earlier onset group examined 1980–1996: 18 vs. 43% (49).

When an incident cohort of children was examined for retinopathy after 6 yr duration, the relative effects of age and puberty could be compared. Seven-field stereoscopic fundal photography was performed with early retinopathy defined as one microaneurysm or hemorrhage, which was present in 24%. Comparing children before and after 11 yr, retinopathy was present in 8 vs. 25%; and comparing children before and after puberty, it was present in 12 vs. 29%. The incident cohort was diagnosed in 1990–1992 and examined in 1996–1998 when their median HbA1c was 8.7% (21).

More recent data using the same methods in mid-adolescence (median age 16.4 yr) with median diabetes duration of 8.6 yr demonstrated that retinopathy declined from 53% (in 1990–1994) to 23% (2000–2004) and then to 12% (2005–2009) (5). In a younger group aged 11–17 yr (median age 14.5 yr, duration 2–5 yr), the prevalence of mild background retinopathy declined from 16% in 1990–1994 to 7% in 2003–2006 (6). Furthermore, those with shorter duration had

considerably less retinopathy, and retinopathy was present in only 6% of the youngest group (aged 11–13 yr) over the whole time of observation.

Laser treatment for retinopathy

Once vision-threatening retinopathy (severe non-proliferative retinopathy or PDR) has been detected, the treatment options are limited. Panretinal photocoagulation, commonly known as ‘laser therapy’, consists of multiple discrete outer retinal burns throughout the mid and far peripheral area but sparing the central macula. It has been proven to reduce the progression of visual loss by more than 50% in patients with PDR (50, 56). There are benefits of early panretinal photocoagulation at the severe nonproliferative retinopathy stage and other factors, such as poor compliance with follow up, impending cataract extraction or pregnancy, and status of fellow eye will help in determining the timing of the panretinal photocoagulation. However, photocoagulation is not indicated for eyes with mild or moderate non-PDR (57). Side effects of treatment are decreased night and peripheral vision and subtle changes in color perception. Complications of laser therapy are vitreal and choroidal hemorrhages or visual sequelae of misplaced burns.

For DME without foveal center involvement when no vision loss has occurred, focal laser photocoagulation to leaking microaneurysms is indicated. For DME with center involvement and vision loss, consideration should be given for intraocular anti-vascular endothelial growth factor (VEGF) therapy (13, 62).

Diabetic nephropathy

Diabetic nephropathy is defined as persistent proteinuria >500 mg/24 h or albuminuria >300 mg/24 h and is usually associated with hypertension, and a diminishing glomerular filtration rate (GFR) (58). End-stage renal failure may occur many years later and requires dialysis or kidney transplantation. Diabetic nephropathy is a major cause of morbidity and mortality among young adults with type 1 diabetes (59). Recent data have suggested that in the absence of diabetic nephropathy mortality, mortality in patients with type 1 diabetes is similar to that in the general population, whereas it is significantly higher in subjects with abnormal urinary AER (60, 61).

Early detection of diabetic nephropathy and timely treatment of blood pressure have a pivotal role in the prevention of end-stage renal failure in young people and adults with diabetes (62) E.

Assessment of incipient nephropathy

The first clinical sign is elevation of albumin excretion. This is generally defined as any of those below (63):

- AER between 20 and 200 $\mu\text{g}/\text{min}$
- AER between 30 and 300 $\text{mg}/24\text{ h}$ in 24 h or timed urine collections
- Albumin concentration 30–300 mg/L (early morning urine sample)
- ACR 2.5–25 mg/mmol or 30–300 mg/g in males and 3.5–25 mg/mmol in females (because of lower creatinine excretion)

Timed overnight or 24 h collections are more burdensome and add little to prediction or accuracy (64).

In the recent American Diabetes Association Clinical practice recommendations, the terms ‘microalbuminuria’ and ‘macroalbuminuria’ have been replaced by two levels of persistent albuminuria (30–299 $\text{mg}/24\text{ h}$ and $>300\text{ mg}/24\text{ h}$), to emphasize the continuous nature of albumin excretion as a risk factor for nephropathy and macrovascular disease.

Other definitions have also been used, in longitudinal studies. The relationship between timed overnight urine collections with first morning urine ACR has now been determined in children and adolescents by linear regression: AER 20–200 mg/min corresponds to ACR of 3.5–35 mg/mmol in males and 4.0–35 mg/mmol for females (33, 59). This also corresponds to 2.4 and 2.2 standard deviations above the mean of the general population.

Microalbuminuria is confirmed by finding two or all of three samples abnormal over a 3- to 6-month period. Persistent microalbuminuria has been shown to predict the progression to end stage renal failure (2, 48, 50, 65–67) and is associated with an increased risk of macrovascular disease (68, 69).

An increase of AER within the microalbuminuric range identifies patients at risk of progression to renal damage (41, 70, 71). Loss of nocturnal dipping on 24 h blood pressure monitoring is an early marker of diabetic renal disease, preceding microalbuminuria (72). Microalbuminuria can also regress (73), especially in adolescents (41, 74). Progression to microalbuminuria is preceded by renal hypertrophy (75).

Confounders exercise increases the AER in the non-diabetic individual and more markedly in diabetes. Even moderate exercise may interfere with the interpretation of data (58). For interpretation of persistently elevated AER values, especially in children with short diabetes duration it is essential to exclude other causes of albuminuria such as immunoglobulin A (IgA) or other types of nephritis common in childhood.

In an incident cohort, after 6-yr duration, early elevation of AER ($>7.5\mu\text{g}/\text{min}$) was examined as an even earlier marker of renal dysfunction. Comparing children before and after 11 yr, elevated AER was present in 5% compared with 25%; and comparing children before and after puberty, it was present in 5% compared with 26% (21). There has been no secular reduction in AER or microalbuminuria in the same cohort that has shown a reduction in retinopathy: 24–22% in the short duration cohort (2- to <5 -yr duration) (6); 45–30% in the cohorts with median duration 8.6 yr (5).

Antihypertensive treatment for prevention of nephropathy

Effective antihypertensive therapy in patients with nephropathy prolongs the time to end-stage renal disease (76). A recent prospective study has shown improved prognosis of renal function from 5 to 7 yr from onset of nephropathy to a median of 21.7 yr (77), predominantly due to aggressive antihypertensive treatment, with smaller contributions from improved glycemic control and smoking cessation (78).

BP values between the 90th and 95th percentiles are defined as prehypertension (79–81). Protocols and reference values for 24 h ambulatory blood pressure monitoring in children have also been published (38, 72). ACEI are recommended for use in children and adolescents with hypertension (79). They have been effective and safe in children in short-term studies (46, 82). The clinical beneficial effect of angiotensin II receptor antagonists in hypertension is similar to that observed with ACEI, but have not been used extensively in children.

In adults, ACEI and ARBs reduce progression from microalbuminuria to macroalbuminuria and increase the regression rate to normoalbuminuria (83, 84). A recent systematic review and meta-analysis has shown that in subjects with diabetes, only ACEI can prevent the doubling of serum creatinine compared with placebo (85). In addition, in placebo controlled studies, only ACEI (at the maximum tolerable dose) were found to significantly reduce the risk of all-cause mortality (86).

Despite the above evidence mainly in adults, there are still some concerns regarding the use of ACEI in protecting long-term renal function in young people without hypertension. In meta-analysis of individual patient data, the beneficial effects were more modest in those with the lowest levels of microalbuminuria (87). Young people with microalbuminuria would potentially be taking ACEI for decades. Side effects include cough, hyperkalemia, headache, and impotence (83, 88). A key safety issue related to the use of ACEI, as well as to ARBs, is the potential risk of congenital

malformation when used during pregnancy. A recent systematic review has highlighted that fetal exposure to ACEI or ARBs has serious neonatal and long-term complications and recommend to improve the awareness of these potential deleterious effects (89). Therefore, when starting treatment with these drugs in adolescent girls, they need to be aware of this risk and birth control measure need to be recommended.

Diabetic neuropathy

Diabetes can affect the somatic and autonomic nervous system. The somatic neuropathies associated with diabetes fall into two broad categories: focal/multifocal and generalized (90).

Focal neuropathies include mononeuropathies such as carpal tunnel syndrome, palsy of the peroneal nerve, palsy of the third cranial nerve, and proximal nerve conditions (e.g., diabetic amyotrophy).

Diabetic sensorimotor polyneuropathy is the most common generalized neuropathy and, for this reason, the simplified term '*diabetic neuropathy*' is commonly used. It is a polyneuropathy because of the diffuse damage to all peripheral nerve fibers, motor, sensory, and autonomic. Such damage occurs insidiously and progressively and is characterized at first by sensory loss and later by loss of motor function, in a stocking and glove distribution. Small fiber dysfunction precedes large-fiber damage in diabetic sensorimotor polyneuropathy (91).

Autonomic neuropathy can cause postural hypotension, vomiting, diarrhea, bladder paresis, impotence, sweating abnormalities, impaired light reflex, impotence, and retrograde ejaculation. Abnormal heart rate responses and prolonged QT intervals have been associated with increased risk of sudden death (92). While overt autonomic neuropathy is rare in childhood and adolescence, subclinical signs of autonomic dysfunction are common, and can be found soon after diabetes diagnosis. Risk factors for autonomic neuropathy in young people include longer diabetes duration, poor glycemic control, and presence of aldose reductase gene (AKR1B1) polymorphisms, specifically the Z-2/Z-2 genotype. Autonomic dysfunction is accelerated by puberty (93).

Assessment of neuropathy

Clinical assessment involves history taking, especially of numbness, persistent pain, or paresthesia; and physical examination of ankle reflexes, vibration, and light touch sensation (by conventional neurological examination or by graduated monofilaments).

Autonomic nerve tests include: heart rate response to deep breathing, standing from a lying position, Valsalva Manoeuvre, heart rate variation at rest,

QT interval, postural changes in blood pressure, and pupillary responses to light and dark adaptation (93). Peripheral nerve tests include: quantitative vibration and thermal discrimination thresholds and nerve conduction. These are mostly used in research settings. Age and gender specific normal ranges need to be applied where relevant when interpreting results. In youth, prevalence rates of peripheral neuropathy vary from <10% to as high as 27% (5, 94, 95), although some of this variability may relate to different methods of screening in addition to recognized risk factors.

Clinical symptoms of autonomic neuropathy are uncommon in the pediatric population. However, subclinical findings have been reported including significant cardiac autonomic neuropathy detected with heart rate variability studies in youth with type 1 diabetes (96).

Macrovascular disease

The mortality and morbidity of CVD are markedly increased in diabetic individuals compared with the non-diabetic population (97).

Hypertension has a greater impact on CVD in diabetic patients than in non-diabetic individuals (33). BP control (<140/80 mmHg in adults) reduces cardiovascular morbidity and mortality in diabetes (34, 64).

A family history of early CVD (before 55 yr of age), lipid disturbances, type 2 diabetes, hypertension (98), and smoking place the individual with diabetes at higher risk.

Atherosclerosis starts in childhood and adolescence as shown by intima-media thickness of the carotids and aorta (92, 99) and silent coronary atherosclerosis measured by intravascular ultrasound in young adults with childhood onset diabetes (100). Silent coronary atherosclerosis (100) and cardiovascular events (15) are strongly associated with poor glycemic control.

Cholesterol plays an important role in the initiation and progression of atherosclerosis (80). Well controlled type 1 diabetes is not associated with gross blood lipid disturbances, but more advanced lipoprotein subclass examinations reveal atherogenic profiles (35). Poor glycemic control was associated with a potentially more atherogenic lipoprotein profile (101).

Changes in lipids associated with increased cardiovascular risk are also associated with central obesity in type 1 diabetes (as well as type 2 diabetes) (102). Individuals with type 1 diabetes are at risk for hypercholesterolemia; the prevalence approached 50% of young adults in one study (103). The prevalence of elevated non-high-density lipoprotein (non-HDL) cholesterol was 25% in a study of individuals <21 yr of age with type 1 diabetes (104).

Adolescents with type 1 diabetes have higher levels of apoB compared with similar age non-diabetics (105). Studies in adults and adolescents with type 1 diabetes suggest a possible complimentary role for measurement of apoB in addition to screening Low-density lipoprotein cholesterol (106). However, data are insufficient at this time to warrant the addition of apoB screening to current lipid screening guidelines for youth with diabetes.

Management of dyslipidemia

In adults with diabetes, statins are effective in the primary and secondary prevention of major cardiovascular events including vascular mortality, stroke, and limb and coronary revascularization (107, 108). The Heart Protection Study was a 5-yr interventional study of 5963 patients with diabetes, 10% of whom had type 1 diabetes. This effect was independent of glycemic control and cholesterol levels.

Short-term trials have shown that simvastatin, lovastatin, and pravastatin are effective and safe in children and adolescents (109–111). No significant side effects were observed in terms of growth, pubertal Tanner grading, testicular volume, menarche, endocrine function parameters, or liver or muscle enzymes (112). The efficacy and safety of statins in children with type 1 diabetes still need to be determined in randomized trials, as does the age at which treatment should be initiated. Special attention should be paid to symptoms associated with muscles and connective tissues, as there is an increased risk of rhabdomyolysis (113).

High \geq cholesterol is defined as ≥ 2.6 mmol/L (100 mg/dL). If this is present then interventions to improve metabolic control, dietary changes, and increased exercise should be instituted. If the above interventions do not lower LDL cholesterol to < 4.1 mmol/L (or < 3.4 mmol/L/130 mg/dL and one or more CVD risk factors), statins should be considered in children aged > 10 yr, although long-term safety is not established. Lipid target levels are shown in Table 2 and management in Table 3.

Functional changes in cardiac and peripheral vascular function

Diabetes is also associated with changes in cardiac and peripheral vascular function. In adults diabetes is associated with increased cardiovascular risk and altered cardiovascular function independent of hypertension or other coronary artery disease (114). Diastolic dysfunction is characterized by reduced early diastolic relaxation, changes in ventricular filling patterns (115, 116), increases in left ventricular filling pressure during exercise (117), and decreases in resting and exercising end-diastolic volume (EDV) (118). At

Table 2. Target levels for different parameters to reduce the risk of microvascular and CVD in children and adolescents with type 1 diabetes

Parameter	Target level
HbA1c (DCCT standard)	$< 7.5\%$ (< 58 mmol/mol) without severe hypoglycemia
LDL cholesterol	< 2.6 mmol/L (100 mg/dL)
HDL cholesterol	> 1.1 mmol/L (40 mg/dL)
Triglycerides	< 1.7 mmol/L (150 mg/dL)
Blood pressure	< 90 th percentile by age, sex, and height
ACR	$< 130/80$ for adolescents
BMI	< 2.5 – 25 mg/mmol in males
Smoking	None
Physical activity	> 1 h of moderate physical activity daily
Sedentary activities	< 2 h daily
Healthy diet	Caloric intake appropriate for age and normal growth. Fat $< 30\%$ of caloric intake, saturated fat $< 10\%$ of caloric intake. Fiber intake 25–35 g daily. Increased intake of fresh fruit and vegetables.

ACR, albumin/creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3. Recommended threshold values for different parameters primary prevention and intervention

Threshold value	Type of intervention
Blood pressure > 90 th percentile for age, gender, and height	Lifestyle intervention
Blood pressure > 90 th percentile despite lifestyle intervention	ACE inhibitor
Blood pressure > 95 th percentile for age, gender, and height	Lifestyle intervention and ACE inhibitor
LDL cholesterol ≥ 2.6 mmol/L (100 mg/dL)	Dietary and lifestyle intervention
LDL cholesterol ≥ 3.4 mmol/L (130 mg/dL) and one or more CVD risk factors	Statins

ACE, angiotensin converting enzyme inhibitor; CVD, cardiovascular disease; LDL, low-density lipoprotein.

a more advanced stage, these changes are collectively defined as diabetic cardiomyopathy, which may be a precursor to diastolic heart failure (1). Abnormalities in diastolic filling will affect stroke volume and thus cardiac output. Previous studies in diabetic adults have shown that aerobic capacity and left ventricular stroke volume during exercise are associated with diastolic dysfunction in adults (118, 119). Adults with asymptomatic type 1 diabetes have reduced exercise capacity and lower stroke volume at peak exercise compared with non-diabetic peers, limitations that are strongly associated with diastolic dysfunction (119,

120) and reduced EDV during exercise (118, 119). Current evidence suggests that healthy adolescents with diabetes may also have lower aerobic capacity (121, 122) and lower exercise stroke volume (121). In a recent study, 52 type 1 diabetic adolescents (mean duration of diabetes was 6 yr) were assessed at rest and during submaximal exercise (at a fixed heart rate) by cardiac magnetic resonance imaging (123). These data confirmed that not only was there reduced diastolic filling at rest but this was exacerbated with exercise reducing stroke volume further. Moreover peak heart rate (the only other mechanism to increase cardiac output) was lower in adolescents with diabetes suggesting they will have impaired cardiac output which may limit their aerobic capacity. Diastolic filling was associated with HbA1c but not diabetes duration suggesting this could be reversed with improved control. Indeed there are data from adult elite athletes with diabetes; those with better control have better cardiovascular performance compared with those with poorer control.

Similar to adults, peripheral vascular function is also impaired in children and adolescents with type 1 diabetes. Endothelial dysfunction is an early event in the development of atherosclerosis and it occurs early in type 1 diabetes (124–127). It appears to be intimately involved in the pathogenesis of microvascular and macrovascular complications of diabetes (125, 128, 129). Studies looking at flow mediated vasodilatation and glyceryl trinitrate have elegantly demonstrated impaired vasodilatation in children and adolescents (130–133). Associations with both hyperglycemia and hypoglycemia and reduced endothelial function have been made as well as an improvement of endothelial function with folate (131, 134, 135). However, folate supplementation was only successful when folate was deficient, with no effect of folate in vascular function in folate replete children (136). Increased physical activity may also be beneficial although this data remains conflicting. Impaired vasodilation of muscle capillary beds also results in increased SBP and DBP during exercise. This has been demonstrated in maximal and submaximal exercise paradigms (123).

Prevention of the later vascular complications of diabetes would be assisted by the identification of early abnormalities such as those observed in the heart and peripheral vasculature. While better glycemic control has been associated with better cardiac and peripheral vascular function, other strategies improving these early changes will potentially reduce the risk of later microvascular and macrovascular complications.

Type 2 diabetes and complications

Type 2 diabetes in youth is associated with greater risk for microalbuminuria and hypertension (95, 137) than

type 1 diabetes. Neuropathy may also be increased (95, 138). Mortality data of those diagnosed 15–30 yr suggest that mortality is higher in type 2 diabetes than type 1 diabetes, for same level of glycemic control (138). Hence complications screening and attention to risk factors should be more aggressive for youth with type 2 diabetes. In comparison to older people diagnosed with type 2 diabetes youth with type 2 diabetes have greater risk of PDR for the same glycemic control (139).

Conclusions

Complications become less common when diabetes management is optimized. Other modifying factors are blood pressure, weight, smoking, and lipids, which are more significant/important in type 2 diabetes and insulin resistance. Screening for complications is important during adolescence and also to prepare for lifelong screening.

Conflicts of interest

The authors have declared no conflicts of interest.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Other complications and diabetes-associated conditions in children and adolescents

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1–3).

Executive summary and Recommendations

- Monitoring of growth and physical development and the use of growth charts are essential in the continuous care of children and adolescents with type 1 diabetes (E).
- Screening of thyroid function by measurement of thyroid stimulating hormone (TSH) and anti-thyroid peroxidase antibodies is recommended at the diagnosis of diabetes (A) and, thereafter, every second year in asymptomatic individuals without goiter or in the absence of thyroid autoantibodies. More frequent assessment is indicated otherwise (E).
- Screening for celiac disease should be performed at the time of diabetes diagnosis, and every 1–2 yr thereafter (B). More frequent assessment is indicated if the clinical situation suggests the possibility of celiac disease or the child has a first-degree relative with celiac disease (E).

- Screening for celiac disease is based on the detection of Immunoglobulin A (IgA) antibodies: tissue transglutaminase (tTG-A) and/or endomysial (EMA).
- Screening for IgA deficiency should be performed at diabetes diagnosis. In people with confirmed IgA deficiency, screening for celiac disease should be performed using IgG specific antibody tests (tTG IgG and/or EM IgG).
- Children with type 1 diabetes detected to have celiac disease on routine screening should be referred to a pediatric gastroenterologist, where available, and on confirmation of the diagnosis receive education and support from an experienced pediatric dietitian. Educational materials for patients and families should be made available (E).
- Diabetes care providers should be alert for the symptoms and signs of Addison's disease (adrenal

failure) in children and youth with type 1 diabetes although the occurrence is rare (E).

- Prevention of lipohypertrophy includes rotation of injection sites with each injection, using larger injecting zones and non-reuse of needles (E).
- There is no established therapeutic intervention for lipodystrophy, necrobiosis lipoidica, or limited joint mobility (LJM) (E).
- Screening for vitamin D deficiency, particularly in high-risk groups, should be considered in young people with type 1 diabetes and treated using appropriate guidelines (E).

Growth, weight gain, and pubertal development

Monitoring of growth and physical development, using appropriate percentile charts and taking mid-parental height into account, are crucial in the care of children and adolescents with diabetes. This includes plotting of anthropometric measurements prior to diagnosis, where available.

Greater height prior to and at diagnosis of type 1 diabetes has been reported frequently (1–7). The precise mechanism for this and whether or not this increased height is maintained is unclear. However, the observation that younger children have the highest BMI suggests pre-natal or early life triggers influence both height and weight gain before diabetes onset (8, 9), as proposed by the ‘accelerator hypothesis’ (10).

There is considerable evidence that patients with suboptimal glycemic control show a decrease in height velocity, while better controlled patients maintain their height advantage (11–13). Insulin is a major regulator of the growth hormone (GH)/insulin-like growth factors (IGFs) axis; adequate insulin secretion and normal portal insulin concentrations are needed to maintain normal serum concentrations of IGFs and IGF-binding proteins, and to promote growth (14). The use of multiple daily insulin injection regimens, insulin analogs, and new technologies including insulin pumps have led to more physiological circulating insulin concentrations, thus improving GH/IGFs alterations (14) and height outcomes, independent of glycemic control (15). The effect of poor glycemic control on growth appears to be exacerbated during puberty, a time of physiological insulin resistance.

Mauriac syndrome, characterized by growth failure, hepatomegaly with glycogenic hepatopathy and steatosis, and late pubertal development, is an uncommon complication in children with persistently poorly controlled diabetes (16, 17). Insulin insufficiency, celiac disease, and other gastrointestinal disorders should be considered in this setting.

There is no role for human GH therapy in the poorly growing child with diabetes, unless it is associated with

Other complications and diabetes-associated conditions

GH deficiency (18), however the diagnosis may be hampered by the high levels of GH, low IGF-1 and low GH-binding protein observed in type 1 diabetes (19–24).

Once the child or adolescent has reached a satisfactory weight after diagnosis, excessive weight gain may indicate high energy intake, and this may be related to excessive exogenous insulin. Excessive weight gain is more common during and after puberty, as well as in those with diagnosis of diabetes in puberty (8, 25). The Diabetes Control and Complications Trial and other studies reported increased weight gain as a side effect of intensive insulin therapy with improved glycemic control (12, 25–27). As obesity is a modifiable cardiovascular risk factor, careful monitoring and management of weight gain should be emphasized in diabetes care.

Girls seem to be more at risk of overweight (25), a recognized risk factor for later development of disturbed eating behavior and eating disorders (28, 29). In association with increased weight is also the risk of ovarian hyperandrogenism, hirsutism, and polycystic ovarian syndrome (30–32). In a recent study of hyperandrogenic adolescents with type 1 diabetes, metformin treatment significantly decreased serum androgens compared with placebo. Metformin therapy did not, however, significantly affect clinical parameters, such as hirsutism, ovulation, and glycemic control; but therapy duration of only 9 months is generally thought to not be long enough to impact on hirsutism (33, 34).

As increased doses of insulin are usually required during puberty, it is important to remember to reduce the dose when IGF-1 levels and insulin requirements decline, typically in late adolescence or young adulthood (24, 35).

Associated autoimmune conditions

Diabetes-associated autoantibodies, including islet cell antibodies (ICA), insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD65), the protein tyrosine phosphatase related molecules IA-2 (ICA512) and IA-2β (phogrin), and/or zinc transporter-8 (ZnT-8) are observed in the overwhelming majority of children *en route* to clinical type 1 diabetes (36). A higher proportion of children with type 1 diabetes have also other detectable organ-specific autoantibodies (e.g., thyroid and adrenal) than children from the general population (37–39). GAD and ZnT8A antibodies are associated with thyroid autoimmunity (38).

Family members of children with diabetes are more likely to have autoantibodies and other manifestations of autoimmune disease than the general population (40–42).

Hypothyroidism

Thyroid disease is one of the most common autoimmune diseases in children with type 1 diabetes,

the other being celiac disease. Thyroid disease occurs more frequently in children and adults with type 1 diabetes than in the general population. Primary or subclinical hypothyroidism due to autoimmune thyroiditis occurs in approximately 3–8% of young people with type 1 diabetes (43, 44), with an incidence ranging from 0.3 to 1.1 per 100 patient years (44, 45) of children and adolescents with diabetes. Antithyroid antibodies can be detected in up to 29% of individuals during the first years of type 1 diabetes (37, 44), and are strongly predictive for the development of hypothyroidism, with a risk ratio of approximately 25 (44, 46). Thyroid antibodies are observed more frequently in girls than in boys, often emerging along with pubertal maturation (44) and also associated with age and diabetes duration (44, 46).

Clinical features may include the presence of a painless goiter, increased weight gain, retarded growth, tiredness, lethargy, cold intolerance, dyslipidemia and bradycardia (43). Glycemic control may not be significantly affected.

Hypothyroidism is confirmed by demonstrating a low free thyroxine and a raised TSH concentration. Importantly, compensated hypothyroidism may be detected in an asymptomatic individual with a normal thyroxine level and a modestly increased TSH.

Treatment of thyroid disease in type 1 diabetes is the same as that used in the general population and is based on replacement with oral L-thyroxine (T4) sufficient to normalize TSH levels. This may allow regression of goiter, if present.

Hyperthyroidism

Hyperthyroidism is less common than hypothyroidism in association with type 1 diabetes, with a reported prevalence of 3–6% in children (44), but is still more common than in the general population. It may be due to Graves' disease or the hyperthyroid phase of Hashimoto's thyroiditis.

Hyperthyroidism should be considered if there is unexplained difficulty in maintaining glycemic control, weight loss without loss of appetite, agitation, tachycardia, tremor, heat intolerance, thyroid enlargement, or characteristic eye signs.

Hyperthyroidism is treated with anti-thyroid drugs such as carbimazole or propylthiouracil; carbimazole is the preferred treatment in children due to the increased risk of liver failure in patients treated with propylthiouracil (47). Beta-adrenergic blocking drugs are helpful during the acute phase of thyrotoxicosis to control tachycardia and agitation. Treatment options for persistent or recurrent hyperthyroidism include surgery or radioactive iodine.

Celiac disease

The prevalence of celiac disease ranges from 1–10% of children and adolescents with diabetes with an incidence of approximately 8 per 1000 patients per year (45, 48–51). The risk of celiac disease is inversely and independently associated with age at diagnosis of diabetes, with the greatest risk in those with diabetes diagnosed before 5 yr of age (50–52). While a large proportion of cases of celiac disease are diagnosed within 2 yr after diabetes presentation and the majority within 10 yr of screening in the pediatric setting, the diagnosis can be made beyond this period (48, 51).

Celiac disease is often asymptomatic (48) and not necessarily associated with poor growth or poor diabetes control (although it should be excluded in such situations). Any child with gastrointestinal signs or symptoms including chronic or intermittent diarrhea and/or constipation, chronic abdominal pain/distention, flatulence, anorexia, dyspeptic symptoms, unexplained poor growth, weight loss, recurrent aphthous ulceration, or anemia should be investigated (50). Undiagnosed celiac disease has also been associated with increased frequency of hypoglycemic episodes and a progressive reduction in insulin requirement over a 12-month period prior to diagnosis (53).

Screening for celiac disease is based on the detection of IgA antibodies (tTG-A and/or EMA); both tests demonstrate sensitivity and specificity >90% (45). Antibodies against deamidated forms of gliadin peptides may also improve the specificity of testing for celiac disease (55). Laboratories reporting celiac disease-specific antibody test results for diagnostic use should continuously participate in quality control programs at a national or international level. Recent guidelines recommend testing for HLA-DQ2 and HLA-DQ8 because celiac disease is unlikely if both haplotypes are negative (56). Adding non-human leukocyte antigen (non-HLA)-susceptible variants to common HLA testing can further improve celiac disease risk prediction (57). However, in people with diabetes, the type 1 diabetes risk alleles (DR3 and DR4) are in linkage disequilibrium with DQ2 and DQ8 and therefore HLA genotyping is likely to exclude celiac disease in only a small proportion of patients (58).

IgA deficiency (which is present in 1:500 in the general population) is more common in people with type 1 diabetes and those with celiac disease (59). Therefore some guidelines recommend routine measurement of total IgA to exclude IgA deficiency, while an alternative strategy is to measure IgA only if the initial screening test using tTG-A and/or EMA is negative. If the child is IgA deficient, IgG-specific antibody tests (tTG or EM IgG, or both) need to be used for screening. This is important because celiac

disease may be more common in those with IgA deficiency than in the general population (60).

In the presence of an elevated antibody level, a small bowel biopsy is needed to confirm the diagnosis of celiac disease by demonstrating subtotal villus atrophy, as outlined in the Marsh Classification (61). For symptomatic children with high tTG-A titers (>10 times the upper limit of normal), recent guidelines recommend that celiac disease can be diagnosed without duodenal biopsy, if the endomysial IgA level is also positive and the patient carries HLA DQ2 or DQ8 (56, 62). Such a change in practice, which is inconsistent with other guidelines (63), will require prospective evaluation to become generally accepted.

A gluten-free diet normalizes the bowel mucosa and frequently leads to disappearance of antibodies, but may not necessarily lead to improved glycemic control (50, 64). The aims of the gluten-free diet include reduction of the risk of subsequent gastrointestinal malignancy and conditions associated with subclinical malabsorption (osteoporosis, iron deficiency, and growth failure) (50, 65, 66). Long-standing celiac disease may be associated with an increased risk of retinopathy (67), while non-adherence to a gluten free diet may increase the risk of microalbuminuria (68).

Children with proven celiac disease should be referred to a pediatric gastroenterologist, where available, and receive education and support from an experienced pediatric dietitian. Educational materials for patients and families should be made available.

Vitiligo

Vitiligo is an acquired pigmentary disorder characterized by a loss of melanocytes resulting in white spots or leukoderma (69). It is a common autoimmune condition associated with type 1 diabetes and is present in approximately 1–7% of people with type 1 diabetes (70). Treatment is difficult and multiple therapies have been tried with little success. Patients should be advised to avoid the sun and to use broad-spectrum sunscreen. As vitamin D deficiency is common in people with vitiligo, measurement of 25-hydroxyvitamin D levels and supplementation should be considered (71). For localized vitiligo, topical corticosteroids may be effective.

Primary adrenal insufficiency (Addison's disease)

Up to 2% of patients with type 1 diabetes have detectable anti-adrenal autoantibodies (37, 72, 73). The HLA DRB1*04-DQB1*0302 (primarily DRB1*0404) and DRB1*0301-DQB1*0201 haplotypes define high-risk subjects for adrenal autoimmunity (74), while homozygosity for the major histocompatibility complex (MHC) (HLA) class I chain-related gene A

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(MICA) polymorphism 5.1 defines those at highest risk for progression to overt Addison's disease (75). Addison's disease may be associated with type 1 diabetes as part of the autoimmune polyglandular syndromes (APS-1 and APS-2) (76). APS 1, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), often presents in childhood and is characterized by the development of adrenal insufficiency, chronic mucocutaneous candidiasis, and hypoparathyroidism. It is caused by a mutation in the autoimmune regulator gene (AIRE) on chromosome at chromosome 21q22.3 (77, 78). In APS-2 (also known as Schmidt Syndrome), the combination of adrenal insufficiency and type 1 diabetes is more common not only in adults (79), but is also seen in children in association with autoimmune thyroiditis (80).

Addison's disease is suspected by the clinical picture of frequent hypoglycemia, unexplained decrease in insulin requirements, increased skin pigmentation, lassitude, weight loss, hyponatremia, and hyperkalemia. The diagnosis is based on the demonstration of a low cortisol response to stimulation with Adrenocorticotropic hormone (ACTH) and evaluation for the presence of adrenal antibodies, although a negative antibody result does not exclude adrenal pathology. Treatment with a glucocorticoid is urgent and lifelong. In some cases the therapy has to be supplemented with a mineralocorticoid such as fludrocortisone.

In asymptomatic children with positive adrenal antibodies detected on routine screening, a rising ACTH level suggests a failing adrenal cortex and the development of primary adrenal insufficiency.

The immunodysregulation polyendocrinopathy X-linked syndrome (IPEX) is another rare disorder associated with diabetes in early childhood, severe enteropathy, and autoimmune symptoms due to a mutation in the forkhead box P3 (*FOX-P3*) gene, which encodes a transcription factor essential for the development and function of regulatory T cells (81, 82).

Lipodystrophy (lipoatrophy and lipohypertrophy)

Lipoatrophy is now seen infrequently with the use of human insulin, and is reported in <1% of patients with type 1 diabetes (83). Case reports have described lipoatrophy in patients treated with insulin analogs, including lispro, glargine, aspart, and detemir (84–86), but it is still a rare side effect. Lipoatrophy has also been described in association with Hashimoto's thyroiditis and celiac disease; the authors speculated that an immune complex-mediated inflammation may contribute to the development of lipoatrophy (87).

Lipohypertrophy is a frequent complication of insulin therapy. Its detection requires both visualization and palpation of injecting sites, as some lesions

can be more easily felt than seen. Normal skin can be pinched tightly together, while lipohypertrophy cannot (88). Lipohypertrophy has been found in up to 48% of those with type 1 diabetes and is associated with higher hemoglobin A1c (HbA1c), greater number of injections, and longer duration of diabetes (83, 89, 90). Lack of rotation of injection sites, use of small injection zones and reusing needles have been consistently reported as independent risk factors for lipohypertrophy (88, 89), while needle length does not have a recognized association. Not only is it unsightly, but insulin may be absorbed erratically and unpredictably from these areas, affecting blood glucose control (91). Treatment of lipohypertrophy involves avoidance of the affected sites for at least 2–3 months, while prevention strategies include rotation of injection sites with each injection, using larger injecting zones and non-reuse of needles.

Necrobiosis lipoidica diabetorum

These are well circumscribed, raised reddish lesions sometimes progressing to central ulceration, usually seen in the pretibial region. The reported prevalence in children varies from 0.06 to 1.6% (92, 93). The etiology is not clearly understood but microangiopathy is thought to play a significant role (93). Necrobiosis lipoidica has been associated with underlying microvascular complications including retinopathy and nephropathy (94, 95). A wide variety of treatments have been used, mostly in adults and with limited efficacy, including: topical, systemic or intra-lesional steroids, aspirin (with or without dipyridamole), cyclosporin, mycophenolate, nicotinic acid, excision and grafting, laser surgery, hyperbaric oxygen, topical granulocyte macrophage colony-stimulating factor, and photochemotherapy with topical Psoralen plus ultraviolet A light (PUVA) (93, 96). Few of the treatment have been evaluated in randomized controlled trials and many have significant side effects (93).

Limited joint mobility

LJM is a bilateral painless, but obvious, contracture of the finger joints and large joints, associated with tight waxy skin. Following its initial description in the 1970s in association with short stature and early microvascular complications, it was observed as a common feature of type 1 diabetes (97, 99). However, more recent studies indicate LJM is present in a minority (~4%) of adolescents with type 1 diabetes (100). There was a >4 fold reduction in frequency of LJM between the mid-70s and mid-90s, in children (101) and a lesser decline in adults (102), with a marked decrease in severity in the fewer children who were affected, most likely the result of improved glucose control during this era.

A simple examination method is to have the patient attempt to approximate palmar surfaces of the interphalangeal joints (103). Passive examination is essential to confirm that inability to do so is due to LJM. With rare exception, LJM appears after the age of 10 yr. The interval between the detection of mild LJM and progression to moderate or severe changes in those who progress beyond mild changes, ranges from a few months to 4 yr, following which stabilization occurs (86).

Skin biopsy specimens have shown active fibroblasts and extensive collagen polymerization in the rough endoplasmic reticulum (104). The biochemical basis for LJM is likely glycation of protein with the formation of advanced glycation end products (AGE). This results in increased stiffness of the periarticular and skin collagen with decreased range of motion. Fluorescence of skin collagen, reflecting the accumulation of stable end products of the glycation reaction, with increased crosslinking, dehydration, and condensation of collagen, increases linearly with age but with abnormal rapidity in type 1 diabetes and is correlated with the presence of retinopathy, nephropathy, vascular disease and LJM (105,106).

Similarly, LJM is associated with a twofold to fourfold risk for retinopathy, nephropathy, and neuropathy (98, 99, 107). Although cross-sectional studies showed no relationship to glycemic control as measured by HbA1c, a longitudinal study of average HbA1c from onset of diabetes showed that for every unit increase in average HbA1c, there was an approximately 46% increase in the risk of developing LJM (108).

Edema

Generalized edema due to water retention is a rare complication of insulin therapy, particularly in young people (109, 105). Edema may be seen during establishment of improved glycemic control after initial diagnosis and after prolonged periods of poor metabolic control, particularly if there has been significant omission of insulin (111). The edema spontaneously resolves over a period of days to weeks with continued good glycemic control. In severe cases, ephedrine has been an effective treatment (112).

Bone health

Type 1 diabetes is associated with osteoporosis and an increased fracture risk, although data in young people with type 1 diabetes are limited (113). Abnormal bone accrual (density and quality) in type 1 diabetes likely has a multifactorial etiology, involving reduced bone formation and abnormal bone quality (114). Two major determinants of bone strain in children are muscle pull and growth. Insulin is anabolic to muscle as well as bone, with many of the factors

detrimental to bone development potentially impacting on muscle or the relationship between muscle and bone. Comorbidities such as celiac disease and thyroid dysfunction can also negatively affect bone health in type 1 diabetes, but the true extent of their impact in children and adolescents is unclear. Therefore, assessment of bone health using bone densitometry should be considered in late adolescence in youth with long duration of type 1 diabetes, especially if complicated by celiac disease. Screening for vitamin D deficiency, particularly in high-risk groups, should be considered in young people with type 1 diabetes and treated using appropriate guidelines (115, 116).

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Conflicts of interest

The authors have declared no conflicts of interest.

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