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2018 Clinical Practice Guidelines

Type 1 Diabetes in Children and Adolescents

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Suspicion of diabetes in a child should lead to immediate confirmation of the diagnosis and initiation of treatment to reduce the likelihood of diabetic ketoacidosis.
- Management of pediatric diabetic ketoacidosis differs from diabetic ketoacidosis in adults because of the increased risk for cerebral edema. Pediatric protocols should be used.
- Children should be referred for diabetes education, ongoing care and psychosocial support to a diabetes team with pediatric expertise.

KEY MESSAGES FOR PEOPLE WITH CHILDREN AND ADOLESCENTS WITH DIABETES

- When a child is diagnosed with type 1 diabetes, the role of a caregiver becomes more important than ever. Family life and daily routines may seem more complicated in the beginning but, over time, and with the support of a diabetes team, these improve. Families discover that a child can have a healthy and fulfilling life with diabetes.

Note: Unless otherwise specified, the term “child” or “children” is used for individuals 0 to 18 years of age, and the term “adolescent” for those 13 to 18 years of age.

Introduction

Diabetes mellitus is the most common endocrine disease and one of the most common chronic conditions in children. Type 2 diabetes and other types of diabetes, including genetic defects of beta cell function, such as monogenic and neonatal diabetes, are being increasingly recognized in children and should be considered when clinical presentation is atypical for type 1 diabetes (for additional details see Definition, Classification and Diagnosis of Diabetes, Pre-diabetes and Metabolic Syndrome chapter, p. S10). This section addresses those areas of type 1 diabetes management that are specific to children.

Education

Children with new-onset type 1 diabetes and their families require intensive diabetes education by an interprofessional pediatric diabetes health-care (DHC) team that should include either a pediatric endocrinologist or pediatrician with diabetes expertise, dietitian, diabetes nurse educator, social worker and mental health professional to provide them with the necessary skills and knowledge to manage this disease. The complex physical, developmental and emotional needs of children and their families necessitate specialized care to ensure the best long-term outcomes (1,2). Education topics must include insulin action, administration and dosage adjustment; blood glucose (BG) and ketone monitoring; sick-day management and prevention of diabetic ketoacidosis (DKA); nutrition therapy; physical activity; and prevention, detection and treatment of hypoglycemia.

Anticipatory guidance and healthy behaviour counselling should be part of routine care, especially during critical developmental transitions (e.g. daycare, school entry, adolescence). Health-care providers should regularly initiate discussions with children and their families about school, diabetes camp, psychological issues, fear of hypoglycemia, substance use, obtaining a driver's license and career choices. Behavioural interventions that have been applied broadly to clinic-based populations with a focus on improving self-efficacy and self-management skills have shown little benefit on improving glycemic control, but may improve caregiver coping skills and reduce parent-child conflict, emphasizing the need for a continuing programme of education (3–5).

Children with new-onset diabetes who present with DKA require a short period of hospitalization to stabilize the associated metabolic derangements and to initiate insulin therapy. Outpatient education for children with new-onset diabetes has been shown to be less expensive than inpatient education and associated with similar or slightly better outcomes when appropriate interprofessional resources to provide outpatient education on basic diabetes management are available (6,7).

Glycemic Targets

Improved metabolic control reduces both the onset and progression of diabetes-related complications in adults and adolescents with type 1 diabetes (8,9). Knowledge of glycemic targets by

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Table 1
Recommended glycemic targets for children and adolescents with type 1 diabetes

Age (years)	A1C (%)	Fasting/preprandial PG (mmol/L)	2-hour postprandial PG* (mmol/L)	Considerations
<18	≤7.5	4.0–8.0	5.0–10.0	Caution is required to minimize severe or excessive hypoglycemia. Consider preprandial targets of 6.0–10.0 mmol/L as well as higher A1C targets in children and adolescents who have had severe or excessive hypoglycemia or have hypoglycemia unawareness.

A1C, glycated hemoglobin; PG, plasma glucose.

* Postprandial monitoring is rarely done in young children except for those on continuous subcutaneous insulin infusion (CSII) therapy for whom targets are not available.

the child with diabetes and parents and consistent target setting by the diabetes health-care team have been shown to be associated with improved metabolic control (10). Aggressive attempts should be made to reach the recommended glycemic target outlined in Table 1; however, clinical judgement is required to determine which children can reasonably and safely achieve these targets without severe or recurrent hypoglycemia. Results from a large multicentre observational study found that glycated hemoglobin (A1C) targets of ≤7.5% can be safely achieved without an increase in the risk of severe hypoglycemia in children less than 6 years of age (11). In some follow-up studies, episodes of severe hypoglycemia have been associated with poorer cognitive function, such as with memory and learning, whereas other studies have found that chronic hyperglycemia and glycemic variability in young children (ages 4 to 10 years) are associated with white matter structural changes and poorer overall cognitive performance (12–15). Young age at diabetes onset (under 7 years of age) has also been associated with poorer cognitive function (16). Treatment goals and strategies must be tailored to each child, with consideration given to individual risk factors.

Insulin Therapy

Insulin therapy is the mainstay of medical management of type 1 diabetes. A variety of insulin regimens can be used, but few have been studied specifically in children with new-onset diabetes. The choice of insulin regimen depends on many factors, including the child's age, duration of diabetes, family lifestyle, school support, socioeconomic factors, and family, patient, and physician preferences. Regardless of the insulin regimen used, all children should be treated to meet glycemic targets.

The honeymoon period, which can last up to 2 years after diagnosis, is characterized by target glycemic control and low insulin requirements (<0.5 units/kg/day). At the end of this period, more intensive management may be required to continue meeting glycemic targets. Two methods of intensive diabetes management have been used: basal-bolus regimens (long-acting basal insulin analogues and rapid-acting bolus insulin analogues) and continuous subcutaneous insulin infusion (CSII) therapy. Basal-bolus therapy has resulted in improved control over traditional twice-daily neutral protamine Hagedorn (NPH) and rapid-acting bolus analogue therapy in some but not all studies (17–19).

CSII is safe and effective and can be initiated at any age (20–22). A Cochrane review found that CSII resulted in slightly improved

metabolic control over basal-bolus therapy (23). Some clinic-based studies of CSII in school-aged children and adolescents have shown a significant reduction in A1C with reduced hypoglycemia 12 to 24 months after initiation of CSII when compared to pre-CSII levels (24) or in the longer term when compared to controls on injections (25). Young age, A1C at CSII initiation and number of daily boluses may be associated with improved or sustained near-normal metabolic outcome (26). The Sensor-Augmented Pump Therapy for A1C Reduction (STAR) 3 study demonstrated that sensor-augmented insulin-pump therapy was more effective in lowering A1C levels than multiple daily injections (MDI) in children with poorly controlled type 1 diabetes mellitus (27).

Most, but not all, pediatric studies of the long-acting basal insulin analogues (detemir, glargine and degludec) have demonstrated improved fasting blood glucose (FBG) levels and fewer episodes of nocturnal hypoglycemia with a reduction in A1C (17,28–32). Two large population-based observational studies have not found improved A1C in children with diabetes using basal-bolus therapy or CSII when compared to those using NPH and rapid-acting bolus analogues (33,34). Insulin therapy should be individualized to reach A1C targets, minimize hypoglycemia and optimize quality of life.

Glucose Monitoring

Self-monitoring of blood glucose (SMBG) is an essential part of management of type 1 diabetes, and increased frequency has been associated with better clinical outcomes (35–37). Evidence of a strong association between frequency of SMBG and hemoglobin A1C levels has been found in T1D Exchange Clinic Registry participants (37). Subcutaneous continuous glucose sensors allow detection of asymptomatic hypoglycemia and hyperglycemia. In some studies, use of continuous glucose monitoring (CGM) has resulted in improved glycemic control with less hypoglycemia (38–40). In 1 larger randomized controlled trial of 322 adults and children, use of CGM was associated with improved glycemic control in adults but not in children and adolescents (41). Glycemic benefit correlated with duration of sensor use, which was much lower in children and adolescents (42). Recently, a built-in algorithm in an available CSII device with low glucose suspend feature has been shown to significantly lower overnight hypoglycemia (43,44).

Closed-Loop Pancreas System

The closed-loop pancreas system, also known as the artificial or bionic pancreas system, is one of the most rapidly evolving areas of clinical care for type 1 diabetes. It couples the use of an insulin pump with infusion of 1 or more hormones (insulin +/- glucagon), a glucose sensor and an algorithm for glucose control. The closed-loop system allows for decreasing excursions in blood glucose levels while reducing the overall burden of self-care. However, the system must ensure patient safety as well as prevent the occurrence of severe hypo- and hyperglycemia, as well as DKA. Results from several studies are promising for outcomes combining a lowering of the number of hypoglycemic events while optimizing per cent time in target range for glucose, fasting blood glucose and mean sensor glucose (45). However, most studies are short term and assessed the closed-loop system in different clinical settings. Larger randomized clinical trials in adults and youth are currently underway.

Nutrition

All children with type 1 diabetes should receive counselling from a registered dietitian experienced in pediatric diabetes. Children with

Table 2
Examples of carbohydrates for treatment of mild-to-moderate hypoglycemia

Patient age	<5 yrs	5 to 10 yrs	>10 yrs
Amount of carbohydrate	5 g	10 g	15 g
Carbohydrate Source			
Glucose tablet (4 g)	1	2 or 3	4
Dextrose tablet (3 g)	2	3	5
Apple or orange juice; regular soft drink; sweet beverage (cocktails)	40 mL	85 mL	125 mL

diabetes should follow a healthy diet as recommended for children without diabetes in *Eating Well with Canada's Food Guide* (46). This involves consuming a variety of foods from the 4 food groups (grain products, vegetables and fruits, milk and alternatives, and meat and alternatives). Children with diabetes have been found to consume a diet that is similar to children without diabetes, one that is higher in fat and lower in fibre than guidelines recommend for healthy eating (47). Carbohydrate counting is a commonly used method of matching insulin to carbohydrate intake that allows increased flexibility in diet, although fat and protein content also influence postprandial glucose levels. There is no strong evidence that one form of nutrition therapy is superior to another in attaining age-appropriate glycemic targets. Nutrition therapy should be individualized (based on the child's nutritional needs, eating habits, lifestyle, ability and interest) and must ensure normal growth and development without compromising glycemic control. This plan should be evaluated regularly and at least annually. Features suggestive of eating disorders and of celiac disease should be systematically sought out (48).

Treatment of Hypoglycemia

Hypoglycemia is a major obstacle for children with type 1 diabetes and can affect their ability to achieve glycemic targets. Children with early-onset diabetes are at greatest risk for disruption of cognitive function and neuropsychological skills, but the respective roles of hypoglycemia and hyperglycemia in their development are still questioned (16,49). Significant risk of hypoglycemia often necessitates less stringent glycemic goals, particularly for younger children. There is no evidence in children that one insulin regimen or mode of administration is superior to another for resolving nonsevere hypoglycemia. As such, treatment must be individualized (50). Frequent use of CGM in a clinical care setting may reduce episodes of hypoglycemia (51).

Severe hypoglycemia should be treated with pediatric doses of intravenous dextrose in the hospital setting or glucagon in the home setting. In children, the use of mini-doses of glucagon has been shown to be useful in the home management of mild or impending hypoglycemia associated with inability or refusal to take oral carbohydrate. A dose of 10 micrograms (mcg) per year of age (the equivalent of 1 unit on the syringe per year of age) (minimum dose 20 mcg (2 units), maximum dose 150 mcg (15 units)) is effective at treating and preventing hypoglycemia, with an additional doubled dose given if the BG has not increased in 20 minutes (52,53). Treatment of mild hypoglycemia is described in Table 2.

Chronic Poor Metabolic Control

A careful multidisciplinary assessment should be undertaken for every child with chronically poor metabolic control (e.g. A1C >10%) to identify potential causative and associated factors, such as depression (54), eating disorders (55), lower socioeconomic status, lower family support and higher family conflict (56,57), and to identify

and address barriers to improved glycemic control. Use of a standardized measure of risk factors has been shown to identify those at high risk for poor control, emergency room visits and DKA (58). Glycemic control may be particularly challenging during adolescence due to physiologic insulin resistance, depression and other psychological issues, and reduced adherence during a time of growing independence. Multipronged interventions that target emotional, family and coping issues have shown a modest reduction in A1C with reduced rates of hospital admission (59–61).

Physical Activity

Inadequate levels of physical activity are common in all children, including those with diabetes. Increased physical activity is associated with better metabolic control. Two recent systematic reviews with meta-analyses have shown A1C reductions of ~0.5% with interventions aimed at increasing physical activity (62,63).

DKA

DKA occurs in approximately 40% of children with new-onset diabetes (range of 28% to 40% across United States centres and 11% to 67% across European centres), and at a frequency of one to 10 episodes per 100 patient-years in those with established diabetes (64,65). DKA continues to be the leading cause of morbidity and mortality in children with diabetes; subtle, persistent changes in brain structure and function ensuing from DKA are being increasingly appreciated (66–68). Children younger than 3 years of age and from areas with low prevalence of diabetes are especially at risk for moderate-to-severe DKA at the time of diagnosis (65). DKA can be prevented through earlier recognition and initiation of insulin therapy. Public awareness campaigns about the early signs of diabetes have significantly reduced the frequency of DKA in new-onset diabetes (69,70). In children with established diabetes, DKA results from failing to take insulin or poor sick-day management. Sick-day management includes more frequent SMBG, ketone measurement during hyperglycemia and adjustment of insulin dose in response to monitoring (71). Risk is increased in children with poor metabolic control or previous episodes of DKA, peripubertal and adolescent girls, children on CSII or long-acting basal insulin analogues, ethnic minorities, and children with psychiatric disorders and those with difficult family circumstances (72–75). The frequency of DKA in established diabetes can be decreased with education, behavioural intervention and family support (76,77), as well as access to 24-hour telephone services or telemedicine for parents of children with diabetes (78–80).

Management of DKA

While most cases of DKA are corrected without event, 0.5% to 1% of pediatric cases are complicated by cerebral edema (81), which is associated with significant morbidity (21% to 35%) and mortality (21% to 24%) (82). In contrast, cerebral edema has rarely been reported in adults (82). Although the cause of cerebral edema is still unknown, several factors are associated with increased risk (Table 3) (83–87). A bolus of insulin prior to infusion is not recommended since it does not offer faster resolution of acidosis (88,89) and may contribute to cerebral edema (90). Early insulin administration (within the first hour of fluid replacement) may increase the risk for cerebral edema (87). Special caution should be exercised in young children with DKA and new-onset diabetes or a greater degree of acidosis and extracellular fluid volume depletion because of the increased risk of cerebral edema.

Table 3
Risk factors for cerebral edema during treatment of diabetic ketoacidosis in children

- Younger age (<5 years)
- New-onset diabetes
- Greater severity of acidosis (lower pH and bicarbonate)
- High initial serum urea
- Low initial partial pressure of arterial carbon dioxide (pCO₂)
- Rapid administration of hypotonic fluids
- IV bolus of insulin
- Early IV insulin infusion (within first hour of administration of fluids)
- Failure of serum sodium to rise during treatment
- Use of bicarbonate

IV, intravenous.

In some centres, it is common practice to initiate an intravenous insulin infusion at a rate of 0.05 units/kg/hour. One recent, prospective randomized controlled study suggests that an initial insulin infusion rate of 0.05 units/kg/hour is safe and effective, but this lower starting rate was not studied among those presenting in more severe or complicated DKA (91). Either mannitol or hypertonic saline can be used in the treatment of cerebral edema, but there is still insufficient evidence to favor one over the other; hypertonic saline use has been associated with increased mortality in a single, retrospective study (92). DKA should be managed according to published protocols for management of pediatric DKA (Figure 1) (93).

Vaccination

Historically, national guidelines have recommended influenza vaccination for children with type 1 diabetes (94,95). Currently, there is no evidence supporting increased morbidity or mortality from influenza in children with type 1 diabetes (96,97). However, the management of type 1 diabetes can be complicated by illness, requiring parental knowledge of sick-day management and increased attention during periods of illness. For this reason, parents may choose to have their children vaccinated.

Smoking Prevention and Cessation

Smoking is a significant risk factor for both cardiovascular (CV) and microvascular complications of diabetes (98) and, in adolescents, is associated with worse metabolic control (99). Smoking prevention should be emphasized throughout childhood and adolescence. The Canadian Paediatric Society website contains useful resources to promote smoking cessation among adolescents (<http://www.cps.ca/en/documents/position/smoking-cessation>) (100).

Alcohol and Substance Use

Adolescents with diabetes have similar rates of alcohol use and similar or higher rates of illicit drug use compared to adolescents without diabetes (101). Regular counselling should be provided around alcohol and substance use.

Contraception and Sexual Health Counselling

Adolescents with diabetes should receive regular counselling about sexual health and contraception. Unplanned pregnancies should be avoided, as pregnancy in adolescent females with type 1 diabetes with suboptimal metabolic control may result in higher risks of maternal and fetal complications than in older women with type 1 diabetes who are already at increased risk compared to the

general population (102). Oral contraceptives, intrauterine devices and barrier methods can be used safely in the vast majority of adolescents (103).

Psychological Issues

For children, and particularly adolescents, there is a need to identify psychological disorders associated with diabetes and to intervene early to minimize the impact over the course of development. Children and adolescents with diabetes have significant risks for psychological problems, including diabetes distress (104), depression (105), anxiety (105), eating disorders and externalizing disorders (106–110). The risks increase during adolescence and emerging adulthood (111–113). Studies have shown that psychological disorders predict poor diabetes management and control (54,105,114–117) and, consequently, negative medical outcomes (118–121). Conversely, as glycemic control worsens, the probability of psychological problems increases (122).

The presence of psychological symptoms and diabetes problems in children and adolescents is often strongly affected by caregiver/family distress. Research has demonstrated that while parental psychological issues may distort perceptions of the child's diabetes control (123), they are often related to poor psychological adjustment and diabetes control (124–127). Maternal anxiety and depression are associated with poor diabetes control in younger adolescents and with reduced positive affect and motivation in older teens (128).

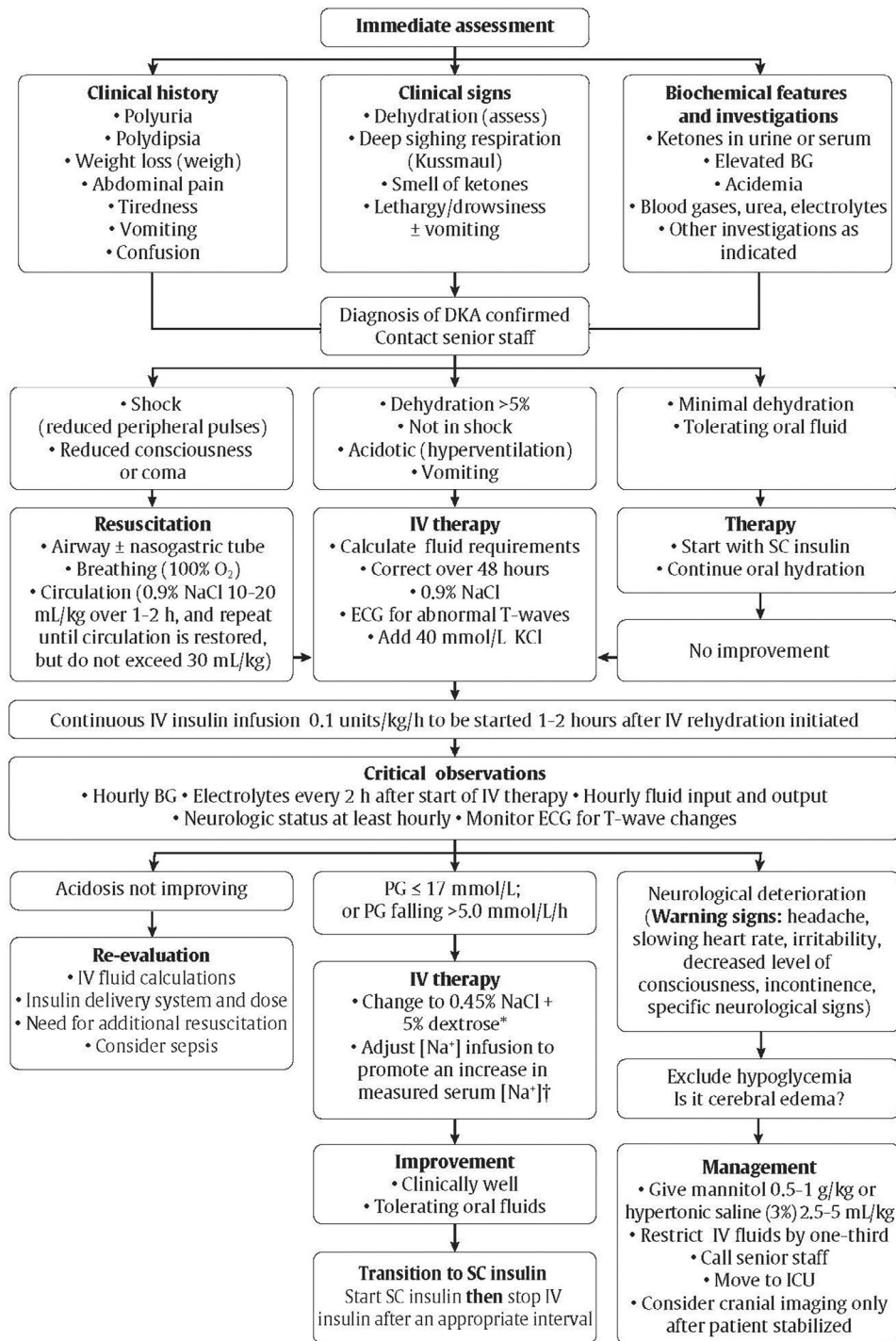
Eating disorders

Ten per cent of adolescent females with type 1 diabetes meet the *Diagnostic and Statistical Manual of Mental Disorders* (4th Edition) criteria for eating disorders compared to 4% of their age-matched peers without diabetes (129). Disordered eating with insulin restriction is also seen in youth with diabetes (130). Furthermore, eating disorders are associated with poor metabolic control (55) and earlier onset and more rapid progression of microvascular complications (131). Eating disorders should be suspected in those adolescent and young adult females who are unable to achieve and maintain metabolic targets, especially when insulin omission is suspected. It is important to identify individuals with eating disorders because different management strategies are required to optimize metabolic control and prevent microvascular complications (129,131,132).

Prevention and intervention

Children and adolescents with diabetes, along with their families, should be screened throughout their development for psychological disorders (133). Given the prevalence of psychological issues, screening in this area can be seen as equally important as screening for microvascular complications in children and adolescents with diabetes (134).

Psychological interventions with children and adolescents, as well as families, have been shown to improve mental health (106,135), including overall well-being and perceived quality of life (136), along with depressive symptoms (137,138). In addition, there is some evidence that psychosocial interventions can positively affect glycemic control (59,135,139). Most importantly, some studies have demonstrated that psychological interventions can increase diabetes treatment adherence, improve glycemic control and improve psychosocial functioning (140,141).



*Increase dextrose content to D10 or D12.5, rather than reducing insulin, to prevent rapid decreases in glucose.

[†]It is acceptable to continue to use 0.9% NaCl to prevent decreases in serum [Na⁺].

Figure 1. Immediate assessment and management of diabetic ketoacidosis in children.

BG, blood glucose; D5W, 5% dextrose in water; D10W, 10% dextrose in water; D12.5W, 12.5% dextrose in water; DKA, diabetic ketoacidosis; ECG, electrocardiogram; ICU, intensive care unit; IV, intravenous; NaCl, sodium chloride; PG, plasma glucose; SC, subcutaneous. Adapted with permission from reference 93.

Comorbid Conditions

Autoimmune thyroid disease

Clinical autoimmune thyroid disease (AITD) occurs in 15% to 30% of individuals with type 1 diabetes (142). The risk for AITD during

the first decade of diabetes is directly related to the presence or absence of anti-thyroid antibodies (i.e. thyroid peroxidase antibodies) at diabetes diagnosis (143). Hypothyroidism is most likely to develop in girls at puberty (144). Early detection and treatment of hypothyroidism will prevent growth failure and symptoms of hypothyroidism (Table 4). Hyperthyroidism also occurs more

Table 4
Recommendations for screening for comorbid conditions in children with type 1 diabetes

Condition	Indications for screening	Screening test	Frequency
Autoimmune thyroid disease	All children with type 1 diabetes	Serum TSH level + thyroid peroxidase antibodies	At diagnosis and every 2 years thereafter; thyroperoxidase antibodies do not need to be repeated if previously positive
	Positive thyroid antibodies, symptoms of thyroid disease or goiter	Serum TSH level (+thyroid peroxidase antibodies if previously negative)	Every 6–12 months
Primary adrenal insufficiency	Unexplained recurrent hypoglycemia and decreasing insulin requirements	8 AM serum cortisol and serum sodium and potassium	As clinically indicated
Celiac disease	Recurrent gastrointestinal symptoms, poor linear growth, poor weight gain, fatigue, anemia, unexplained frequent hypoglycemia or poor metabolic control	Tissue transglutaminase + immunoglobulin A levels	As clinically indicated

TSH, thyroid-stimulating hormone.

Table 5
Screening for diabetes complications, dyslipidemia and hypertension in children with type 1 diabetes

Complication/Comorbidity	Indications and intervals for screening	Screening method
Nephropathy	<ul style="list-style-type: none"> Yearly screening commencing at 12 years of age in those with duration of type 1 diabetes >5 years 	<ul style="list-style-type: none"> First morning (preferred) or random urine ACR Abnormal ACR requires confirmation at least 1 month later with a first morning ACR and, if abnormal, followed by timed, overnight or 24-hour split urine collections for albumin excretion rate Repeated sampling should be done every 3–4 months over a 6- to 12-month period to demonstrate persistence
Retinopathy	<ul style="list-style-type: none"> Yearly screening commencing at 15 years of age with duration of type 1 diabetes >5 years Screening interval can increase to 2 years if good glycemic control, duration of diabetes <10 years and no retinopathy at initial assessment 	<ul style="list-style-type: none"> 7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard); or Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil; or Digital fundus photography
Neuropathy	<ul style="list-style-type: none"> Children ≥15 years with poor metabolic control should be screened yearly after 5 years of type 1 diabetes 	<ul style="list-style-type: none"> Question and examine for symptoms of numbness, pain, cramps and paresthesia, as well as skin sensation, vibration sense, light touch and ankle reflexes
Dyslipidemia	<ul style="list-style-type: none"> Delay screening post-diabetes diagnosis until metabolic control has stabilized Screen at 12 and 17 years of age <12 years of age: screen only those with BMI >97th percentile, family history of hyperlipidemia or premature CVD 	<ul style="list-style-type: none"> Fasting or non-fasting TC, HDL-C, TG, calculated LDL-C. Measurement of non-fasting lipids may be considered if TG are not elevated.
Hypertension	<ul style="list-style-type: none"> Screen all children with type 1 diabetes at least twice a year 	<ul style="list-style-type: none"> Use appropriate cuff size

ACR, albumin to creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; HDL-C; high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

frequently in association with type 1 diabetes than in the general population.

Primary adrenal insufficiency (Addison's disease)

Primary adrenal insufficiency is rare, even in those with type 1 diabetes (145). Targeted screening is required in those with unexplained recurrent hypoglycemia and decreasing insulin requirements (Table 4).

Celiac disease

Celiac disease can be identified in 4% to 9% of children with type 1 diabetes (142), but in 60% to 70% of these children, the disease is asymptomatic (silent celiac disease). Children with type 1 diabetes are at increased risk for classic or atypical celiac disease during the first 10 years of diabetes (146). There is good evidence that treatment of classic or atypical celiac disease with a gluten-free diet improves intestinal and extraintestinal symptoms (147), and prevents the long-term sequelae of untreated classic celiac disease (148). However, there is no evidence that untreated asymptomatic celiac disease is associated with short- or long-term health risks (149,150) or that a gluten-free diet improves health in these individuals (151). Thus, universal screening for and treatment of asymptomatic celiac disease remains controversial (Table 4).

Diabetes Complications

There are important age-related considerations regarding surveillance for diabetes complications and interpretation of investigations (Table 5). Risk for microvascular complications accelerates through puberty (152,153). In an observational study, children with type 1 diabetes with a mean duration of 7.9 years were found to have an age-adjusted prevalence of diabetic nephropathy of 5.8%, retinopathy 5.6%, peripheral neuropathy 8.5%, arterial stiffness 11.6%, hypertension 10.1% and cardiovascular (CV) autonomic neuropathy 14.4% (154).

Chronic kidney disease

Prepubertal children and those in the first 5 years of diabetes should be considered at very low risk for albuminuria (152,155). A first morning urine albumin to creatinine ratio (ACR) has high sensitivity and specificity for the detection of albuminuria (156,157). Although screening with a random ACR is associated with greater compliance than with a first morning sample, its specificity may be compromised in adolescents due to their higher frequency of exercise-induced proteinuria and benign postural proteinuria. Abnormal random ACRs (i.e. >2.5 mg/mmol) require confirmation with a first morning ACR or timed overnight urine collection (158).

The likelihood of transient or intermittent albuminuria is higher during the early peripubertal years (155). Individuals with intermittent albuminuria may progress to overt nephropathy (159). Abnormal screening results require confirmation and follow up to demonstrate persistent abnormalities, as albuminuria can and is more likely to regress in youth compared to older adults (160–162).

Treatment is indicated only for those adolescents with persistent albuminuria. One short-term randomized controlled trial in adolescents demonstrated that angiotensin-converting enzyme (ACE) inhibitors were effective in reducing albuminuria compared to placebo (163). However, there are no long-term intervention studies assessing the effectiveness of ACE inhibitors or angiotensin receptor blockers (ARBs) in delaying progression to overt nephropathy in adolescents with albuminuria. Therefore, treatment of adolescents with persistent albuminuria is based on the effectiveness of treatments in adults with type 1 diabetes (164).

Retinopathy

Retinopathy is rare in prepubertal children with type 1 diabetes and in postpubertal adolescents with good metabolic control (153,165–167). Earlier reductions in A1C during adolescence and attention to blood pressure (BP) control may stave off sight-threatening diabetic retinopathy in adulthood (153).

Neuropathy

When present, neuropathy is mostly subclinical in children (168). While prospective nerve conduction studies and autonomic neuropathy assessment studies have demonstrated increased prevalence of abnormalities over time (169), persistence of abnormalities is an inconsistent finding (170). There are very few studies assessing the diagnostic utility of noninvasive screening methods in children with diabetes; among them, vibration and monofilament testing have suboptimal sensitivity and specificity in adolescents. Normative thresholds vary with age and gender (171). With the exception of intensifying diabetes management to achieve and maintain glycemic targets, no other treatment modality has been studied in children and adolescents.

Dyslipidemia

Most children with type 1 diabetes should be considered at low risk for cardiovascular disease (CVD) associated with dyslipidemia (172–174). The exceptions are those with longer duration of disease, microvascular complications or other CV risk factors, including smoking, hypertension, obesity (175) and/or family history of premature CVD (176). Dyslipidemia screening should be targeted at those greater than 12 years of age and younger children with specific risk factors for dyslipidemia. Measurement of non-fasting lipids is now recommended for adults as long as triglycerides are not elevated. Evidence in children with diabetes is limited. Statin therapy has been studied specifically in children with diabetes, and while there is no evidence linking specific low-density lipoprotein cholesterol (LDL-C) cut-offs in children with diabetes with long-term outcomes, statin therapy has been shown to significantly lower LDL-C as well as lipoproteins (177). In pubertal children without diabetes but with familial hypercholesterolemia, statin therapy is known to be safe and effective at lowering LDL-C levels and attenuating progression of surrogate markers for future CVD (178). Different markers of future CVD are being explored to better predict when to intervene (179–182).

Hypertension

Up to 16% of adolescents with type 1 diabetes have hypertension (183). Twenty-four hour ambulatory BP monitoring has been

used to exclude white coat hypertension and to identify loss of diurnal systolic rhythm (nondippers) with nocturnal hypertension in some normotensive adolescents with type 1 diabetes (184). These abnormalities may be predictive of future albuminuria (184). However, the role of ambulatory BP monitoring in routine care remains uncertain. Children with type 1 diabetes and confirmed hypertension should be treated according to the guidelines for children without diabetes (185).

Transition to Adult Care

Emerging adulthood, the developmental stage between ages 18 to 25 years, is a stage of life wherein the emerging adult is establishing his or her autonomy, personal identity, and making vocational and educational choices (186). For the emerging adult with diabetes, this stage is complicated by the transition from pediatric to adult care, a high-risk period characterized by inadequate medical follow up and self-management, deteriorating glycemic control, and an increased risk of adverse outcomes (187–190). Between 25% and 65% of young adults have no medical follow up during the transition from pediatric to adult diabetes care services (191–193). Those with no follow up are more likely to experience hospitalization for DKA during this period. Organized transition services may decrease the rate of loss of follow up and the risk of adverse outcomes (189,192,195–198). Further, initiating a transition plan in early adolescence (e.g. 12 years of age), that includes education in self-care behaviours, transition readiness assessments and identifying transition goals may be of benefit in preparing adolescents and their families for transition (199,200).

RECOMMENDATIONS

Delivery of Care

1. All children with diabetes should have access to an experienced pediatric DHC team that includes either a pediatric endocrinologist or pediatrician with diabetes expertise, dietician, diabetes nurse educator, social worker and mental health professional for specialized care starting at diagnosis [Grade D, Level 4 (1)].
2. Children with new-onset type 1 diabetes who are medically stable should receive their initial education and management in an outpatient setting, provided that appropriate personnel and daily communication with a DHC team are available [Grade B, Level 1A (6,7)].
3. To ensure ongoing and adequate diabetes care, adolescents should receive care from a specialized program aimed at creating a well-prepared and supported transition to adult care that is initiated early and includes a transition coordinator; patient reminders; and support and education promoting autonomy and self-care management skills [Grade C, Level 3 (189,191,192,194–197)].

Glycemic Targets

4. Children and adolescents <18 years of age should aim for an A1C target $\leq 7.5\%$ [Grade D, Consensus]
 - a. Attempts should be made to safely reach the recommended glycemic target, while minimizing the risk for severe or recurrent hypoglycemia. Treatment targets should be tailored to each child, taking into consideration individual risk factors for hypoglycemia [Grade D, Consensus]
 - b. In children <6 years of age, particular care to minimize hypoglycemia is recommended because of the potential association in this age group between severe hypoglycemia and later cognitive impairment [Grade D, Level 4 (15)].
5. Children with persistently poor glycemic control (e.g. A1C >10%) should be assessed with a validated tool by a specialized pediatric DHC team for comprehensive interdisciplinary assessment and referred for

psychosocial support as indicated [Grade D, Consensus]. Intensive family and individualized psychological interventions aimed at improving glycaemic control should be considered to improve chronically poor metabolic control [Grade A, Level 1A (59–61)].

Insulin Therapy

6. Children with new-onset diabetes should be started on boluses of rapid-acting insulin analogues combined with basal insulin (e.g. intermediate-acting insulin or long-acting basal insulin analogue) using an individualized regimen that best addresses the practical issues of daily life [Grade D, Consensus].
7. Insulin therapy should be assessed at each clinical encounter to ensure it still enables the child to meet A1C targets, minimizes the risk of hypoglycemia and allows flexibility in carbohydrate intake, daily schedule and activities [Grade D, Consensus]. If these goals are not being met, an intensified diabetes management approach (including increased education, monitoring and contact with diabetes team) should be used [Grade A, Level 1 (8) for adolescents; Grade D, Consensus for younger children], and treatment options may include the following:
 - a. Increased frequency of injections [Grade D, Consensus]
 - b. Change in the type of basal and/or bolus insulin [Grade B, Level 2 (29) for adolescents; Grade D, Consensus for younger children]
 - c. Change to CSII therapy [Grade C, Level 3 (22)].

Treatment of Hypoglycemia

8. In children, the use of mini doses of glucagon (10 mcg per year of age with minimum dose 20 mcg and maximum dose 150 mcg) should be considered in the home management of mild or impending hypoglycemia associated with inability or refusal to take oral carbohydrate [Grade D, Level 4 (52)].
9. In the home situation, severe hypoglycemia in an unconscious child >5 years of age should be treated with 1 mg glucagon subcutaneously or intramuscularly. In children ≤5 years of age, a dose of 0.5 mg glucagon should be given. The episode should be discussed with the DHC team as soon as possible and consideration given to reducing insulin doses for the next 24 hours to prevent further severe hypoglycemia [Grade D, Consensus].
10. Dextrose 0.5 to 1 g/kg should be given intravenously over 1–3 minutes to treat severe hypoglycemia with unconsciousness when intravenous access is available [Grade D, Consensus].

Physical Activity

11. Regular physical activity ≥3 times per week for ≥60 minutes each time should be encouraged for all children with diabetes [Grade A, Level 1 (62,63)].

Diabetic Ketoacidosis

12. To prevent DKA in children with diabetes:
 - a. Targeted public awareness campaigns should be considered to educate parents, other caregivers (e.g. teachers) and health-care providers about the early symptoms of diabetes [Grade C, Level 3 (70,76)]
 - b. Immediate assessment of ketone and acid-base status should be done in any child presenting with new-onset diabetes [Grade D, Consensus]
 - c. Comprehensive education and support services [Grade C, Level 3 (77)], as well as 24-hour telephone services [Grade C, Level 3 (78)], should be available for families of children with diabetes.
13. DKA in children should be treated according to pediatric-specific protocols [Grade D, Consensus]. If appropriate expertise/facilities are not available locally, there should be immediate consultation with a centre with expertise in pediatric diabetes [Grade D, Consensus].
14. In children in DKA, rapid administration of hypotonic fluids should be avoided [Grade D, Level 4 (84)]. Circulatory compromise should be treated with only enough isotonic fluids to correct circulatory inadequacy [Grade D, Consensus]. Replacement of fluid deficit should be extended over a 48-hour period with regular reassessments of fluid status [Grade D, Level 4 (84)].
15. In children in DKA, an intravenous insulin bolus should not be given [Grade D, Consensus]. The insulin infusion should not be started for at least 1 hour after starting fluid replacement therapy [Grade D, Level 4 (87)]. An

intravenous infusion of short-acting insulin should be used at an initial dose of 0.05 to 0.1 units/kg/h, depending on the clinical situation [Grade A, Level 1A (91)].

16. In children in DKA, once blood glucose reaches ≤17.0 mmol/L, intravenous dextrose should be started to prevent hypoglycemia. The dextrose infusion should be increased, rather than reducing insulin, to prevent rapid decreases in glucose. The insulin infusion should be maintained until pH normalizes and ketones have mostly cleared [Grade D, Consensus].
17. In children in DKA, administration of sodium bicarbonate should be avoided except in extreme circulatory compromise, as this has been associated with cerebral edema [Grade D, Level 4 (83)].
18. In children in DKA, either mannitol or hypertonic saline may be used in the treatment of cerebral edema [Grade D, Level 4 (92)].

Microvascular Complications

19. Children ≥12 years with diabetes duration >5 years should be screened annually for CKD with a first morning urine ACR (preferred) [Grade B, Level 2 (157)] or a random ACR [Grade D, Consensus]. Abnormal results should be confirmed [Grade B, Level 2 (161,162)] at least 1 month later with a first morning ACR and, if abnormal, followed by timed, overnight or 24-hour split urine collections for albumin excretion rate [Grade D, Consensus]. Albuminuria (ACR >2.5 mg/mmol; AER >20 mcg/min) should not be diagnosed unless it is persistent, as demonstrated by 2 consecutive first morning ACR or timed collections obtained at 3- to 4-month intervals over a 6- to 12-month period [Grade D, Consensus].
20. Children ≥12 years with persistent albuminuria should be treated per adult guidelines (see Chronic Kidney Disease in Diabetes chapter, p. S201) [Grade D, Consensus].
21. Children ≥15 years with 5 years' diabetes duration should be annually screened and evaluated for retinopathy by an expert professional [Grade C, Level 3 (167)]. The screening interval can be increased to every 2 years in children with type 1 diabetes who have good glycaemic control, duration of diabetes <10 years and no significant retinopathy (as determined by an expert professional) [Grade D, Consensus].
22. Children ≥15 years with 5 years' diabetes duration and poor metabolic control should be questioned about symptoms of numbness, pain, cramps and paresthesia, and examined for skin sensation, vibration sense, light touch and ankle reflexes [Grade D, Consensus].

Comorbid Conditions and Other Complications

23. Children and adolescents with diabetes, along with their families, should be screened regularly for psychosocial or psychological disorders [Grade D, Consensus] and should be referred to an expert in mental health and/or psychosocial issues for intervention when required [Grade D, Consensus].
24. Adolescents with type 1 diabetes should be regularly screened using nonjudgmental questions about weight and body image concerns, dieting, binge eating and insulin omission for weight loss [Grade D, Consensus].
25. Children with type 1 diabetes who are <12 years of age should be screened for dyslipidemia if they have other risk factors, such as obesity (body mass index >97th percentile for age and gender) and/or a family history of dyslipidemia or premature CVD. Routine screening for dyslipidemia should begin at 12 years of age, with repeat screening after 5 years [Grade D, Consensus].
26. Once dyslipidemia is diagnosed in children with type 1 diabetes, the dyslipidemia should be monitored regularly and efforts should be made to improve metabolic control and promote healthy behaviours. While it can be treated effectively with statins, a specific LDL cut-off to initiate treatment is yet to be determined in this age category [Grade D, Consensus].
27. All children with type 1 diabetes should be screened for hypertension at least twice annually [Grade D, Consensus].
28. Children with type 1 diabetes and BP readings persistently above the 95th percentile for age should receive healthy behaviour counselling, including weight loss if overweight [Grade D, Level 4 (201)]. If BP remains elevated, treatment should be initiated based on recommendations for children without diabetes [Grade D, Consensus].

29. Influenza vaccination should be offered to children with diabetes as a way to prevent an intercurrent illness that could complicate diabetes management [Grade D, Consensus].
30. Formal smoking prevention and cessation counselling should be part of diabetes management for children with diabetes [Grade D, Consensus].
31. Adolescents should be regularly counselled around alcohol and substance use [Grade D, Consensus].
32. Adolescent females with type 1 diabetes should receive counselling on contraception and sexual health in order to prevent unplanned pregnancy [Grade D, Level 4 (202)].
33. Children with type 1 diabetes who have anti-thyroid antibodies should be considered at high risk for autoimmune thyroid disease [Grade C, Level 3 (143)]. Children with type 1 diabetes should be screened at diabetes diagnosis with repeat screening every 2 years using a serum thyroid-stimulating hormone and thyroid peroxidase antibodies [Grade D, Consensus]. More frequent screening is indicated in the presence of positive anti-thyroid antibodies, thyroid symptoms or goiter [Grade D, Consensus].
34. Children with type 1 diabetes and symptoms of classic or atypical celiac disease (see Table 4) should undergo celiac screening [Grade D, Consensus] and, if confirmed, be treated with a gluten-free diet to improve symptoms [Grade D, Level 4 (147)] and prevent the long-term sequelae of untreated classic celiac disease [Grade D, Level 4 (148)]. Discussion of the pros and cons of screening and treatment of asymptomatic celiac disease should take place with children and adolescents with type 1 diabetes and their families [Grade D, Consensus].

Abbreviations

A1C, glycated hemoglobin; ACR, albumin to creatinine ratio; ACE, angiotensin-converting enzyme; AER, albumin excretion rate; AITD, autoimmune thyroid disease; ARB, angiotensin receptor blocker; BP, blood pressure; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CSII, continuous subcutaneous insulin infusion; DHC, diabetes health care; DKA, diabetic ketoacidosis; LDL-C, low-density lipoprotein cholesterol; MDI, multiple daily injections; mcg, micrograms; SMBG, self-monitoring of blood glucose.

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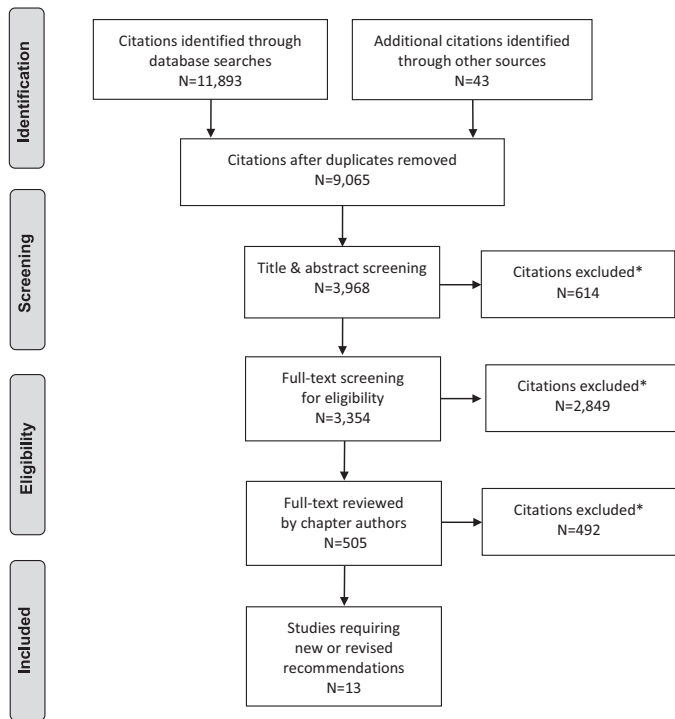
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Literature Review Flow Diagram for Chapter 34: Type 1 Diabetes in Children and Adolescents



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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