

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

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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-2 β (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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