

ISPAD Clinical Practice Consensus Guidelines 2006–2007

Other complications and associated conditions

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Impaired growth and development

Monitoring of growth and development and the use of percentile charts is a crucial element in the care of children and adolescents with diabetes.

Increased height at diagnosis of type 1 diabetes mellitus (T1DM) has been frequently reported (1–4). The precise mechanism for this and whether or not this increased height is maintained is unclear. Some studies report that poorly controlled patients show a decrease in height standard deviation score over the next few years, while better controlled patients maintain their height advantage (3, 4). Others have not shown this relationship with diabetic control (1).

In a recent study from Australia, children treated with modern regimens (diagnosed after 1990) maintained their increased height better than children diagnosed before 1991 (2). Although the median haemoglobin A1c (HbA1c) did not differ significantly, those diagnosed after 1990 had a significantly higher number of insulin injections per day.

Poor gain of height and weight, hepatomegaly (non-alcoholic steatosis hepatitis) and late pubertal development (Mauriac's syndrome) have been reported in children with persistently poorly controlled diabetes. Insulin insufficiency, coeliac disease and other gastrointestinal disorders should be considered in this setting. Growth hormone (GH) levels are high in poorly controlled diabetes mellitus, but insulin-like growth factor (IGF)-1 levels are decreased. Thus, GH therapy is contraindicated in the children with poorly controlled T1DM. The possible uses of IGF-1 in T1DM are the subject of considerable investigation.

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 (5). The Diabetes Control and Complications Trial and other studies have reported increased weight gain as a side-effect of intensive insulin therapy with improved metabolic control (6–8). 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 being overweight and developing eating disorders as well. In association with increased weight is the risk of hyperandrogenism and polycystic ovarian syndrome (9).

It is important to remember to reduce the dose of insulin when pubertal development is completed because increased doses of insulin are required during the adolescent growth spurt.

Associated autoimmune conditions

Islet cell antibodies (ICA) as well as autoantibodies to insulin, the 65-kDa isoform of glutamic acid decarboxylase (GAD65) and/or the protein tyrosine phosphatase-related molecules islet antigen-2 (IA-2) (ICA512) and IA-2 β (phogrin) are observed in the overwhelming majority of children *en route* to clinical T1DM (10, 11).

A higher proportion of children with T1DM also have other detectable organ-specific autoantibodies

[e.g., thyroid, tissue transglutaminase (tTG), adrenal] than children from the general population.

Family members of children with diabetes are more likely to have autoantibodies and other manifestations of autoimmune disease than the general population (12, 13).

Hypothyroidism

Primary hypothyroidism caused by autoimmune thyroiditis occurs in approximately 3–8% (14) or 0.9 per 100 patient years (15) of children and adolescents with diabetes. Antithyroid antibodies have been shown to occur during the first years of diabetes in up to 25% of individuals with diabetes (16–20) and to be predictive for the development of clinical or compensated hypothyroidism (20). Thyroid antibodies are observed more frequently in girls than in boys, often emerging along with pubertal maturation (20).

Clinical features may include the presence of a painless goitre, increased weight gain, retarded growth, tiredness, lethargy, cold intolerance and bradycardia. Diabetic control may not be significantly affected.

Hypothyroidism is confirmed by demonstrating a low free thyroxine and a raised thyroid stimulating hormone (TSH) concentration. Compensated hypothyroidism may be detected in an asymptomatic individual with a normal thyroxine level and a modestly increased TSH.

The treatment is based on replacement with oral L-thyroxine (T₄) sufficient to normalize TSH levels and usually this allows regression of the goitre if present.

Hyperthyroidism

Hyperthyroidism is less common than hypothyroidism in association with diabetes (18, 21), but still more common than in the general population. It may be because of Grave's disease or the hyperthyroid phase of Hashimoto's thyroiditis.

Hyperthyroidism should be considered if there is unexplained difficulty in maintaining glycaemic control, weight loss without loss of appetite, agitation, tachycardia, tremor, heat intolerance, thyroid enlargement or characteristic eye signs.

Treatment of hyperthyroidism consists of antithyroid drugs such as carbimazole or propylthiouracil. 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.

Coeliac disease

Coeliac disease occurs in 1–10% of children and adolescents with diabetes or 0.7 per 100 patient years

(15, 22–30). Coeliac disease is often asymptomatic (26, 28, 31) and not necessarily associated with poor growth or poor diabetic control (although it should be excluded in such situations). Any child with gastrointestinal signs or symptoms including diarrhoea, abdominal pain, flatulence, dyspeptic symptoms, recurrent aphthous ulceration, unexplained poor growth or anaemia should be investigated. Undiagnosed coeliac disease has also been associated with increased frequency of hypoglycaemic episodes and a progressive reduction in insulin requirement over a 12-month period prior to diagnosis (32).

The screening for coeliac disease is based on the detection of immunoglobulin (Ig)A antiendomysial (EMA) antibodies and IgA antibodies against tTG. Although experience with a recently introduced assay for tTG antibodies suggests that tTG may be more sensitive than EMA (91 vs. 86%), the latter is slightly more specific for coeliac disease (100 vs. 96%) (33). Antigliadin antibodies might be more sensitive for coeliac disease than EMA and tTg antibodies in very young children (<2 yr), although their specificity remains modest.

IgA deficiency (which is present in 1:500 individuals) should be excluded when screening for coeliac disease by measuring the total IgA level. IgA antibodies may not be detected in IgA deficiency, resulting in a false-negative test. If the child is IgA deficient, then IgG antigliadin and IgG tTG antibodies should be used for screening (34). It is important to remember that coeliac disease is more common in those with IgA deficiency than in the general population (1.7% compared with 0.25%) (35).

In the presence of an elevated antibody level, a small bowel biopsy is needed to confirm the diagnosis of coeliac disease (Marsh classification) (36).

A gluten-free diet normalizes the bowel mucosa and frequently leads to disappearance of antibodies but may not necessarily lead to improved metabolic control (37).

In an asymptomatic child with proven coeliac disease, a gluten-free diet can be considered justified with the aim of reducing the risk of subsequent gastrointestinal malignancy and conditions associated with subclinical malabsorption (i.e., osteoporosis and iron deficiency). While this is a prudent recommendation, there is no literature documenting the long-term benefit of a gluten-free diet in asymptomatic children diagnosed with coeliac disease by routine screening. One paediatric case series has shown an increase in height for weight following the introduction of a gluten-free diet (31). Another demonstrated a non-significant increase in body mass index and a non-significant reduction in HbA1c (38). Some studies have demonstrated short-term benefits in other patient groups in terms of improved well-being and increased bone mineral density (39–41).

The risk of coeliac disease is negatively and independently associated with age at the onset of diabetes, with a threefold higher risk being seen in children aged < 4 yr than in those aged > 9 yr, and girls have a higher risk of having both diseases (42).

Children with proven coeliac disease should be referred to a paediatric gastroenterologist and receive support from a paediatric dietician with experience of gluten-free diets.

Vitiligo

Vitiligo is an acquired pigmentary disorder characterized by a loss of melanocytes, resulting in white spots or leucoderma (43). It is a common autoimmune condition associated with T1DM and is present in about 6% of diabetic children (44). Treatment is difficult and multiple therapies have been tried with little success.

Primary adrenal insufficiency (Addison's disease)

Up to 2% of patients with T1DM have detectable antiadrenal autoantibodies (16, 45, 46). Addison's disease is occasionally associated with T1DM in the autoimmune polyglandular syndromes (APS I and II). APS I is associated with mucocutaneous candidiasis and hypoparathyroidism and is caused by a mutation in the autoimmune regulator gene on chromosome 21q22.3 (47, 48). APS II is more common in adults but is also seen in children in association with autoimmune thyroiditis (49).

The condition is suspected by the clinical picture of frequent hypoglycaemia, unexplained decrease in insulin requirements, increased skin pigmentation, lassitude, weight loss, hyponatraemia and hyperkalaemia.

The diagnosis is based on the demonstration of a low cortisol response to an adrenocorticotrophic hormone (ACTH) test. Treatment with a glucocorticoid is urgent and lifelong. In some cases, the therapy has to be supplemented with a mineralocorticoid.

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 is another rare disorder associated with diabetes in early infancy, severe enteropathy and autoimmune symptoms because of a clear genetic defect (FOX-P3) (50).

Lipodystrophy (lipoatrophy and lipohypertrophy)

Lipoatrophy is now seen infrequently with the use of human insulin. Recent case reports have described

lipoatrophy also occurring in patients on insulin pumps treated with lispro insulin, and in patients treated with Lantus (51–53), it is still a rare side-effect.

Lipohypertrophy is a frequent complication of insulin therapy. It has been found in up to 48% of those with T1DM and has associated with higher HbA1c, more injections and longer duration but not the needle length (54–56).

Non-rotation of injection sites has been consistently reported as an independent risk factor for lipohypertrophy (54, 56). Not only is it unsightly but insulin may also be absorbed erratically and unpredictably from these areas (57, 58).

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 10% (44, 59). The aetiology is not clearly understood. Necrobiosis lipoidica diabetorum has been associated with underlying microvascular complications (60, 61). A wide variety of treatments have been used over the years in adults including topical, systemic or intra-lesional steroids, aspirin, cyclosporin, mycophenolate, becaplermin, excision and grafting, laser surgery, hyperbaric oxygen, topical granulocyte-macrophage colony-stimulating factor and photochemotherapy with topical psoralen and ultraviolet-A radiation (62–69). None has been proven useful in controlled clinical trials, and many of these treatments have significant side-effects.

Limited joint mobility

Limited joint mobility (LJM) is the earliest clinically apparent long-term complication of T1DM in childhood. It is a bilateral painless, but obvious, contracture of the finger joints and large joints, associated with tight waxy skin. Following its initial description associated with short stature, and early microvascular complications, it was recognized to be a common feature of both T1DM and type 2 diabetes mellitus, with a wide range of limitation, affecting ~30% of youngsters and correlating with diminished stature (70, 71). Changes begin in the metacarpophalangeal and proximal interphalangeal joints of the fifth finger and extend radially with involvement of the distal interphalangeal joints as well. Involvement of larger joints includes not particularly the wrist and elbow but also the ankles and cervical and thoracolumbar spine. The limitation is only mildly disabling even when severe.

A simple examination method is to have the patient attempt to approximate palmar surfaces of the interphalangeal joints (72). Passive examination is

essential to confirm that inability to do so is because of LJM. With rare exception, LJM appears after the age of 10 yr. The interval between the detection of mild LJM and the 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 (71).

Skin biopsy specimens have shown active fibroblasts and extensive collagen polymerization in the rough endoplasmic reticulum (73). The biochemical basis for LJM is likely glycation of protein with the formation of advanced glycation end products. 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 cross-linking, dehydration and condensation of collagen, increases linearly with age but with abnormal rapidity in T1DM, correlating with the presence of retinopathy, nephropathy and LJM (74).

LJM is associated with a three- to fourfold risk for retinopathy, nephropathy and neuropathy (71, 75, 76). Although cross-sectional studies showed no relationship to diabetes control as measured by HbA1c, 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 (77).

There has been a more than fourfold reduction in frequency of LJM between the mid-1970s and the mid-1990s in children (78) and a lesser decline in adults (79), with a marked decrease in severity in the fewer children who are affected, most likely the result of improved glucose control during this era.

Oedema

Generalized oedema because of water retention is a rare complication of insulin therapy. Oedema may be seen during establishment of improved glycaemic control after prolonged periods of poor metabolic control, particularly if there has been significant omission of insulin (80, 81). The oedema spontaneously resolves over a period of days to weeks with continued good glycaemic control.

Recommendations

Monitoring of growth and physical development and the use of growth charts is an essential element in the continuous care of children and adolescents with T1DM (E).

Screening of thyroid function by analysing circulating TSH and antibodies is recommended at the diagnosis of diabetes and, thereafter, every second year in asymptomatic individuals without goitre or

in the absence of thyroid autoantibodies. More frequent assessment is indicated otherwise (E).

Screening for coeliac disease should be carried out at the time of diagnosis and every second year thereafter. More frequent assessment is indicated if the clinical situation suggests the possibility of coeliac disease or the child has a first-degree relative with coeliac disease (E).

Children with T1DM detected to have coeliac disease on routine screening should be referred to a paediatric gastroenterologist and on confirmation of the diagnosis should receive support from a paediatric dietician with experience of gluten-free diets (E).

Routine clinical examination should be undertaken for skin and joint changes. Regular screening by laboratory or radiological methods is not recommended. There is no established therapeutic intervention for lipodystrophy, necrobiosis lipoidica or LJM (E).

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