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ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: Other complications and associated conditions in children and adolescents with type 1 diabetes

Farid H. Mahmud[1] | Nancy S. Elbarbary[2] | Elke Fröhlich-Reiterer[3] | Reinhard W. Holl[4] | Olga Kordonouri[5] | Mikael Knip[6] | Kimber Simmons[7] | Maria E. Craig[8,9,10]

[1]Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

[2]Department of Pediatrics, Ain Shams University, Cairo, Egypt

[3]Department of Pediatrics, Medical University of Graz, Graz, Austria

[4]Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany

[5]Children's Hospital auf der Bult, Hannover, Germany

[6]Children's Hospital, University of Helsinki, Helsinki, Finland

[7]Barbara Davis Center for Diabetes, University of Colorado, Denver, Colorado

[8]The Children's Hospital at Westmead, Westmead, NSW, Australia

[9]Discipline of Child and Adolescent Health, University of Sydney, Sydney, NSW, Australia

[10]School of Women's and Children's Health, University of New South Wales, Sydney, NSW, Australia

Correspondence

Prof. Maria Craig, Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia.

Email: m.craig@unsw.edu.au

1 | WHAT'S NEW

- Expanded sections on screening and management of associated conditions (eg, systemic autoimmune diseases) and skin disorders (eg, continuous glucose monitoring [CGM]-related skin issues).
- Revised recommendations for celiac disease screening.

2 | RECOMMENDATIONS

- Regular monitoring of anthropometric measurements and physical development, using growth standards, 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 antithyroid peroxidase antibodies is recommended at the diagnosis of diabetes **(A)** and, thereafter, every second year in asymptomatic individuals. More frequent assessment may be indicated in the presence of symptoms, goiter or positive thyroid autoantibodies **(E)**.
- Screening for celiac disease should be performed at the time of diabetes diagnosis, and at 2 and 5 years thereafter, as it is frequently asymptomatic **(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 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 or EmA IgG, or both) **(B).**
  - Measurement of human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 is rarely helpful to exclude celiac disease in patients with type 1 diabetes and not recommended as a screening test **(B).**
  - Children with type 1 diabetes detected to have positive celiac antibodies on routine screening, should be referred to a pediatric gastroenterologist, as positive serologic testing alone is not diagnostic for celiac disease in this population **(E).**
  - Upon confirmation of the diagnosis of celiac disease, patients should receive educational 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 adrenal insufficiency (due to Addison's disease [AD]) in

children and adolescents with type 1 diabetes although the occurrence is rare **(E).**

- Routine clinical examination should be undertaken for skin (eg, lipodystrophy) and joint changes (eg, limited joint mobility). Regular screening by laboratory or radiological methods is not recommended **(E).**
- Patient education regarding proper injection techniques, rotating injection sites with each injection and non-reuse of needles remain the best strategies to prevent lipohypertrophy or lipoatrophy **(E).**
- Injection sites should be regularly assessed at each clinic visit for lipohypertrophy and lipoatrophy as they are potential causes of glucose variability **(C).**
- Diabetes care providers should be aware of potential skin irritation with use of insulin pumps and continuous glucose monitoring (CGM) by recommending rotation of pump and sensor insertion sites **(E).**
- Screening for vitamin D deficiency, particularly in high risk groups (celiac disease, darker skin pigmentation) should be considered in young people with type 1 diabetes and treated using appropriate guidelines **(E).**

3 | GROWTH, WEIGHT GAIN, AND PUBERTAL DEVELOPMENT

Monitoring of anthropometric measurements and physical development, using age-appropriate standards and taking mid-parental height into account, is a crucial element in the care of children and adolescents with diabetes.

Greater height prior to and at diagnosis of type 1 diabetes has been reported.[1–6] The precise mechanism for this and whether or not this increased height is maintained is unclear[7]; however, the observation that younger children have the highest body mass index (BMI) suggests that prenatal or early life triggers influence both height and weight gain before diabetes onset.[8,9] In children who are autoantibody positive, a sustained increased BMI is associated with an increased risk of progression to type 1 diabetes.[10]

There is considerable evidence that patients with suboptimal glycemic control show a decrease in height velocity, whereas better controlled patients maintain their height advantage.[11–13] Insulin is a major regulator of the growth hormone (GH) and 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 and CGM have led to more physiological circulating insulin concentrations, thus improving GH/IGFs concentrations[14] and height outcomes, independent of glycemic control.[15] The effect of elevated HbA1c on growth appears to be exacerbated during puberty, a time of physiological insulin resistance. Significant impairment in growth during puberty has also been reported particularly in young people developing albuminuria.[16] Mauriac syndrome, characterized by growth failure, hepatomegaly with glycogenic hepatopathy and steatosis, and late pubertal development is an uncommon complication in children with persistently elevated HbA1c.[17,18] Insulin insufficiency, hypothyroidism, celiac disease, and other gastrointestinal disorders should also be considered in this setting. Recently, a mutation in an enzyme of glycogen metabolism (catalytic subunit of glycogen phosphorylase kinase) was reported in a patient with Mauriac syndrome that increases glycogen content by limiting glycogen breakdown and hence increasing its deposition in the human liver. The postulated mechanism is that this mutant enzyme of glycogen metabolism combines with hyperglycemia to directly inhibit glycogen phosphorylase, resulting in many of the phenotypic features observed in this syndrome.[19]

Once the child or adolescent has regained and reached a satisfactory weight after the initial diagnosis of diabetes mellitus, excessive weight gain may indicate high energy intake, and this may be related, in part, to excessive exogenous insulin. Excessive weight gain is more common during and after puberty, especially in girls, as well as in those with diagnosis of diabetes in puberty.[8,20] 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.[12,20–22] Obese children with type 1 diabetes have a higher prevalence of cardiovascular risk factors (hypertension, dyslipidemia, and cardiac autonomic dysfunction) than normal-weight children with type 1 diabetes.[23,24] Given that recent data from multiple international registries show higher rates of overweight and obesity in children and adolescents with type 1 diabetes compared with their non-diabetic peers, careful monitoring and management of weight gain should be emphasized in diabetes care as obesity is a modifiable cardiovascular risk factor.[25,26] Use of adjuvant therapy with insulin sensitizing agents, such as the addition of metformin along with insulin does not improve glycemic control among overweight adolescents with type 1 diabetes; however, it may lead to less insulin requirements and a reduction of BMI.[27]

Girls seem to be more at risk of overweight,[20] a recognized risk factor for later development of eating disorders.[28] In association with increased weight, there is also the risk of ovarian hyperandrogenism, hirsutism, and polycystic ovarian syndrome.[29–31] In a recent study of adolescents with hyperandrogenism and type 1 diabetes, metformin treatment significantly decreased serum androgens compared to 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.[32,33]

Menarche may be delayed in patients who develop type 1 diabetes prior to the onset of puberty, and several studies indicate that this delay is independent of glycemic control.[34,35] Delayed menarche has also been associated with an increased risk of diabetic nephropathy and retinopathy, whereas early menarche was not.[36] In addition, as increased doses of insulin are usually required during puberty, it is important to remember to reduce the dose after pubertal development is completed and insulin resistance has decreased.

3.1 | Associated autoimmune conditions

Children with type 1 diabetes are at increased risk for comorbid autoimmune diseases compared to children in the general population.

Clinicians must be aware of the symptoms and risk factors associated with common comorbid autoimmune diseases so that screening can be performed if there is clinical suspicion for disease outside of the recommended screening intervals. A high proportion of children and adolescents with type 1 diabetes have detectable organ-specific autoantibodies (eg, thyroid, adrenal) in addition to islet autoantibodies, and approximately 25% of patients with type 1 diabetes are diagnosed with another autoimmune disease.[37] Comorbid autoimmune diseases occur more commonly in females compared to males and increase in incidence with age.[37] In situations where laboratory testing is not available or is cost prohibitive, careful monitoring of linear growth and relevant symptoms is important. Screening of common comorbid conditions at regular intervals, such as autoimmune thyroid disease and celiac disease, which may be subclinical or asymptomatic, allows for earlier identification and treatment.

Autoimmune thyroid disease is the most common comorbid autoimmune condition seen in patients with type 1 diabetes, followed by celiac disease.[37] Other autoimmune conditions more commonly diagnosed in patients with type 1 diabetes include primary adrenal insufficiency, collagen vascular disease (eg, rheumatoid arthritis, lupus, psoriasis, scleroderma), other gastrointestinal diseases (eg, Crohn's disease, ulcerative colitis, autoimmune hepatitis, autoimmune gastritis), and skin disease (eg, vitiligo, scleroderma). Rarer autoimmune conditions, such as multiple sclerosis, which have also been associated with type 1 diabetes in childhood and adolescence, will not be described in detail.[38,39]

3.1.1 | Hypothyroidism

Thyroid disease occurs more frequently in children and adults with type 1 diabetes than in the general population. The incidence of autoimmune thyroid disease in children and adolescents ranges from 0.3 to 1.1 per 100 patient years and exists in approximately 3% to 8% of children with type 1 diabetes.[40,41] The prevalence of autoimmune thyroid disease increases with age to approximately 20%, with the majority of patients having hypothyroidism.[37] Antithyroid antibodies can be detected in up to 29% of individuals soon after diagnosis with type 1 diabetes and are strongly predictive for the development of hypothyroidism.[41–43] Antithyroid antibodies are observed more frequently in girls than in boys and are associated with age, diabetes duration, and pubertal maturity.[44] In addition, the presence of islet autoantibodies to GAD (glutamic acid decarboxylase) and ZnT8 (Zinc Transporter-8) are associated with thyroid autoimmunity.[45,46] Screening children for antithyroid antibodies (antithyroid peroxidase and antithyroglobulin) can help stratify which patients to follow most closely for development of hypothyroidism.

Clinical features of hypothyroidism include the presence of a painless goiter, decreased linear growth, fatigue, cold intolerance, bradycardia, and weight gain. Glycemic control may not be significantly affected, but hypoglycemia has been linked to hypothyroidism.[47]

Hypothyroidism is confirmed by demonstrating a low-free T4 level and a raised thyroid stimulating hormone (TSH) concentration. Importantly, thyroid function tests can be misleading if a patient is not metabolically stable (eg, diabetic ketoacidosis) or has suboptimal blood glucose control.[48,49] In thyroid autoantibody positive, asymptomatic individuals, compensated hypothyroidism may also be detected, with a normal free T4 level and a mildly increased TSH. These patients should be closely followed for clinical changes with more frequent thyroid function testing (6-12 months) to detect potential disease progression and the need for treatment.[44]

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 levothyroxine (synthetic T4) to normalize TSH levels. This may allow for regression of goiter, if present. In addition to routine monitoring of TSH, management of treated thyroid disease should include measurement of thyroid function tests 6 weeks after changing levothyroxine dosage and after blood pressure or lipid lowering medications are initiated. It is important to note that untreated hypothyroidism can worsen total cholesterol, low density lipoprotein (LDL) cholesterol, and triglyceride levels.[50] Children should also have their thyroid gland palpated yearly for the development of nodules or cysts that would require further evaluation (Table 1).

3.1.2 | Hyperthyroidism

Hyperthyroidism is less common than hypothyroidism in association with type 1 diabetes, but is still more common than in the general population. The reported prevalence of hyperthyroidism ranges from 0.5% to 6%, with the highest rates reported in children.[37,41,51–53] Hyperthyroidism may be due to Graves' disease or the hyperthyroid phase of Hashimoto's thyroiditis.

Hyperthyroidism is characterized by weight loss, increase in appetite, palpitations, tachycardia, tremors, hyperactivity with difficulty concentrating, heat intolerance, and thyroid enlargement. Characteristic eye findings such as exophthalmos and lid lag may or may not be present in children but are often milder than in adults.[54]

Hyperthyroidism is confirmed with a suppressed TSH and an elevation of one or more measures of thyroid hormone (Free T4 and/or Free T3). Graves' disease is confirmed by the presence of TSH receptor antibodies.

Hyperthyroidism is treated with the antithyroid drugs carbimazole or methimizole, which is the recommended treatment in children due to the increased risk of liver failure in patients treated with propylthiouracil.[55] Beta-adrenergic blocking drugs are helpful during the acute phase of thyrotoxicosis to control tachycardia and agitation. If a patient does not go into remission or cannot be controlled on antithyroid medications, definitive treatment options include thyroidectomy or ablation with radioactive iodine.[56]

3.1.3 | Celiac disease

The prevalence of celiac disease ranges from 1% to 10% among children and adolescents with type 1 diabetes.[40,57–60] A recent international comparison with 53 000 children and adolescents with type 1 diabetes across three continents reported a prevalence of celiac disease of 3.5%, with rates ranging from 1.9% in the United States to 7.7% in Australia.[26] 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 years of age.[59,61,62] Most cases of celiac disease are diagnosed within the first year of diagnosis of diabetes followed by the 2- and 5-year period after

TABLE 1 Summary of common complications and associated conditions in children and adolescents with type 1 diabetes

Comorbid autoimmune disease	Symptoms	Risk factors	Screening and confirmatory tests	Screening recommendations
Hashimoto's thyroiditis	• Decreased linear growth • Painless goiter • Fatigue • Cold intolerance • Bradycardia • Weight gain • Hypoglycemia may occur	• Age • Duration of T1DM • Presence of GAD autoantibodies • Celiac disease	• Antithyroid peroxidase antibodies, antithyroglobulin antibodies, TSH, T4 or free T4	• At diagnosis (after glucose control established): antithyroid peroxidase and antithyroglobulin antibodies, TSH • Every 2 years: TSH (sooner if positive thyroid antibodies at diagnosis or with symptoms)
Graves' disease	• Weight loss • Normal/increased appetite • Palpitations • Heat intolerance • Goiter • Proptosis • Poor glycemic control	• Age • Duration of T1DM • Presence of GAD autoantibodies	• Thyroid stimulating immunoglobulin, TSH, T4 or free T4, T3	• Symptom related
Celiac disease	• Most often asymptomatic • Hypoglycemia • Poor linear growth • Diarrhea • Nausea, vomiting, abdominal pain	• Affected first degree relative • Other autoimmune disease	• Tissue transglutaminase antibody • Anti-endomysial antibody	• At diagnosis • At least after a T1DM duration of 2 and 5 years (sooner if symptomatic or first-degree relative with celiac disease)
Autoimmune gastric disease	• Most often asymptomatic • Anemia (pernicious anemia or iron deficiency anemia)	• Thyroid autoimmunity • Persistence of GAD autoantibodies	• Antiparietal cell autoantibodies • Blood counts, vitamin B12, ferritin, gastrin	• Symptom related
Primary adrenal insufficiency (Addison's disease)	• Hypoglycemia • Fatigue • Nausea • Weight loss • Salt craving • Postural hypotension • Hyperpigmentation of skin and mucosa	• First degree relative with disease	• 21-hydroxylase antibodies, ACTH, fasting am cortisol, electrolytes, plasma renin	• Symptom related
Vitiligo	• Sharply delineated skin depigmentation, affecting extremities, face, and neck and trunk	• Thyroid disorder • polyglandular autoimmune syndrome (PAS) • vitamin D deficiency	• Clinical diagnosis	• Symptom related
Alopecia	• Non-scarring, round and/or oval patches of hair loss	• Polyglandular autoimmune syndrome type 2	• Clinical diagnosis	• Symptom related
Juvenile idiopathic rheumatoid arthritis	• Joint(s) inflammation characterized by swelling, limitation in the range of motion, tenderness; symptoms must be present for at least 6 weeks		• Clinical diagnosis	• Symptom related
Sjogren syndrome	• Xerophthalmia (dry eyes) and xerostomia (dry mouth); recurrent parotitis, with other organ involvement		• Clinical diagnosis	• Symptom related
Psoriasis	• Skin disorder with thick, red, bumpy patches covered with silvery scales		• Clinical diagnosis	• Symptom related
Sarcoidosis	• Non-caseating granulomas, predominantly in the lymph nodes, lungs, eyes and skin.		• Clinical diagnosis	• Symptom related
Sclerodema diabeticorum	• Thickening of the skin with characteristic “peau d'orange” appearance		• Clinical diagnosis	• Symptom related

Abbreviations: GAD, glutamic acid decarboxylase antibodies; T1DM, type 1 diabetes mellitus; TSH, thyroid stimulating hormone; T4, thyroxine; ACTH, adrenocorticotropic hormone.

diabetes presentation and the majority within 10 years of screening in the pediatric setting, but the diagnosis can be made beyond this period into adulthood.[57,59,63]

Celiac disease is often asymptomatic and not necessarily associated with poor growth, deterioration in glycemic control or hypoglycemia,[64–66] although it should be excluded in such situations.[58] The presence of celiac disease should be evaluated in any child with gastrointestinal signs or symptoms including chronic or intermittent diarrhea and/or constipation, chronic abdominal pain/distention, flatulence, anorexia, dyspeptic symptoms and well as recurrent hypoglycemia, anemia, unexplained poor growth, weight loss, or recurrent aphthous ulceration.[62]

Screening for celiac disease is based on the detection of IgA antibodies (tissue transglutaminase [tTG-A] and/or endomysial [EmA]);

both tests demonstrate sensitivity and specificity >90%.[67] Laboratories reporting celiac disease-specific antibody test results for diagnostic use should continuously participate in quality control programs on 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, however, given the high proportion of type 1 diabetes patients who carry these risk alleles, use of HLA as first line testing to screen for celiac disease (CD) in this population may not be practical, nor cost effective.[68–71]

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.[72] 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 EmA 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.[73]

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.[74] Several biopsy samples should be taken from multiple intestinal sites, including the duodenal bulb, as celiac disease can present with variable biopsy findings, and non-focal or "patchy" histopathologic lesions have been observed from duodenal samples in over 50% of children and up to 25% of adults.[75,76]

For clearly 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 EmA IgA level is also positive and the patient carries HLA DQ2 or DQ8 haplotype.[68,77] Such a change in practice, which is inconsistent with other guidelines,[67] will require prospective evaluation to become generally accepted. As most children with type 1 diabetes and positive tTG are asymptomatic, duodenal biopsy is still required in most children. tTG positivity at the time of diagnosis may also be transient emphasizing the need of a duodenal biopsy to verify the diagnosis.[78] Children with coexisting type 1 diabetes and celiac disease have been observed to have low high density lipoprotein (HDL) cholesterol and increased LDL cholesterol, as well as significantly higher rates of concomitant autoimmune thyroid disease indicating a need to assess the serum lipid profile and regularly assess thyroid function in children with both conditions.[79,80]

A gluten-free diet normalizes the bowel mucosa and frequently leads to disappearance of antibodies, but may not necessarily impact glycemic control.[62,65,81] The aims of the gluten-free diet also include reduction of the risk of subsequent gastrointestinal malignancy and conditions associated with subclinical malabsorption that may include osteoporosis, iron deficiency, and growth failure.[60,82,83] Long-standing celiac disease in the context of type 1 diabetes may be associated with an increased risk of retinopathy,[84] while non-adherence to a gluten-free diet may increase the risk of albuminuria.[85,86] In addition to an increased risk for microvascular and potentially for macrovascular complications, premature death has been reported more frequently in T1D patients with comorbid celiac disease.[84] Children and adolescents with T1D, with poor adherence to a gluten-free diet, may also have a reduced quality of life and worse glycemic control.[87]

Children diagnosed with celiac disease should receive education and support from an experienced pediatric dietitian. Educational materials for patients and families should be made available. The prevalence of celiac disease is increased among first-degree relatives of children with type 1 diabetes, particularly in mothers, and consequently family members of a child with newly diagnosed celiac disease should also be screened for tTG.[78]

3.1.4 | Primary adrenal insufficiency (AD)

Up to 2% of patients with type 1 diabetes have detectable antiadrenal autoantibodies.[42,88,89] The HLA DRB1*04-DQB1*0302 (primarily DRB1*0404) and DRB1*0301-DQB1*0201 haplotypes define high-risk subjects for adrenal autoimmunity,[90] while homozygosity for the major histocompatability complex (MHC) (HLA) class I chain-related gene A (MICA) polymorphism 5.1 defines those at highest risk for progression to overt AD.[91] A person with type 1 diabetes who has the DRB*0404 allele and 21-hydroxylase antibodies has a 100-fold risk of developing AD may be associated with type 1 diabetes as part of the autoimmune polyglandular syndromes (APS-1 and APS-2).[92]

AD 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 confirmed by the demonstration of a low morning cortisol in the presence of elevated basal adrenocorticotropic hormone (ACTH), with an inadequate response to an ACTH stimulation test and positive antiadrenal (21-hydroxylase) antibodies. 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.

Autoimmune polyendocrinopathy syndrome type 1 (APS1) is characterized by several endocrine deficiencies including hypoparathyroidism, AD, gonadal failure as well as diabetes; diabetes is generally a later manifestation. This entity is sometimes referred to as autoimmune polyendocrinopathy-candidiasis- ectodermal dystrophy/dysplasia (APECED) syndrome is now known to be due to an inactivating mutation of the *AIRE* (Autoimmune Regulator) gene on chromosome 21. APS2, also known as Schmidt syndrome, is characterized by T1DM, AD, and hypothyroidism, is more common in females and is associated with specific HLA loci. These entities are discussed in greater detail below.[93]

The immunodeficiency, polyendocrinopathy, and enteropathy, X-linked syndrome (IPEX) is an extremely rare monogenic polyendocrine disorder that presents in the perinatal period or infancy with diabetes (with an overall prevalence of 60%) or chronic diarrhea due to autoimmune enteropathy. Other manifestations are eczematous dermatitis, autoimmune hypothyroidism, autoimmune cytopenias, and glomerulonephritis due to a mutation in the forkhead box P3 (FOX-P3) gene, which encodes a transcription factor the development and function of regulatory T-cells.[94]

3.1.5 | Autoimmune gastritis

Parietal cell antibodies are the principal immunological markers of autoimmune gastritis and react against the H^+/K^+ ATPase of the gastric parietal cells.[89,95] Chronic damage to the proton pump may result in hypo/achlorhydria, hypergastrinaemia, and iron deficiency anemia due to decreased gastric secretion and decreased iron absorption.[96] Parietal cell antibodies may also inhibit intrinsic factor secretion, leading to vitamin B12 deficiency and pernicious anemia.[97] Type 1 diabetes is associated with an increased risk of parietal cell antibody positivity,[98] with prevalence rates of parietal cell antibodies in children ranging from 5.3% to 7.5%.[60,99,100] Physicians should be aware of the possibility of parietal cell antibodies in children and adolescents with type 1 diabetes in cases of unclear anemia (microcytic as well as macrocytic) or gastrointestinal symptoms, but routine screening is not recommended.

3.1.6 | Type 1 diabetes and systemic autoimmune diseases

Aside from organ-specific autoimmune diseases, other non-organic-specific or systemic autoimmune diseases, such as juvenile idiopathic rheumatoid arthritis (JIA), Sjogren syndrome, and sarcoidosis may also develop in patients with type 1 diabetes.[22] In children with T1D, JIA is the most frequently encountered non-organ-specific autoimmune condition (see Table 1).[101,102]

3.2 | Type 1 diabetes-related skin conditions

3.2.1 | Lipohypertrophy and lipoatrophy

Lipohypertrophy and lipoatrophy represent well-recognized dermatological complications of subcutaneous insulin administration.[103]

3.2.2 | Lipohypertrophy

Lipohypertrophy is a frequent complication of insulin therapy characterized by fibrous and poorly vascularized lesions in the subcutaneous adipose tissue[104] and is caused by the direct anabolic effect of insulin on local skin leading to fat and protein synthesis and occurs because of repeated injections at the same site.[105] As lipohypertrophied areas are relatively painless, patients often continue to use the same area rather than move to a new painful site. Other possible associated risk factors are longer duration of insulin therapy, high number of insulin injections, and reuse of needles. Initial skin changes can be subtle and manifest only as thickening of skin. This can be easily missed by visual inspection and palpation of areas used for injection is recommended to appreciate the soft, lipoma-like nodules.[106]

Injecting insulin into lipohypertrophic subcutaneous tissue can reduce insulin absorption by up to 25% and alter its duration of action.[107] Individual variability in insulin action is significantly higher in those with lipohypertrophy compared to those without. These factors combine and may result in unpredictable blood glucose levels and unexplained hypoglycemia.[107–109]

Injection sites should be examined regularly at each clinic visit by a health care professional for possible lipohypertrophy or lipoatrophy. Individuals should also be taught to examine their own injection sites and how to detect lipohypertrophy[110,111] and should be advised not to inject into areas of lipohypertrophy until abnormal tissue returns to normal, which will take several months. The best current preventative for lipohypertrophy includes patient education regarding proper injection techniques, rotating injection sites with each injection, and non-reuse of needles.[111]

3.2.3 | Lipoatrophy

Lipoatrophy is a form of localized lipodystrophy and a recognized complication of insulin therapy characterized by a disfiguring loss of subcutaneous fat at the site of insulin injections and appears to be the result of a lipolytic reaction to impurities or other components in some insulin preparations, as its prevalence has fallen to only 1% to 2% of patients with the increasing use of purified insulin.[112,113]

The mechanism of lipoatrophy is generally poorly understood although an immune pathogenesis seems likely, and it is seen more in patients who often have other signs of autoimmunity.[114] Other theories involve cryotrauma from refrigerated insulin, mechanical trauma due to the angle of injection, surface alcohol contamination, or local hyperproduction of tumor necrosis factor alpha from macrophages induced by injected insulin.[108,115] Repeated use of the same insulin injection site for continuous subcutaneous insulin infusion (CSII) or injections and multiple usage of the same pen needle increases the risk of lipoatrophy.[109]

Treatment options are limited and may include changing the site of injection or CSII[116,117] and switching insulin analogues; however, these are not always effective in complete resolution of lesions.[118,119] Treatment with steroids, given orally (daily low-dose prednisolone)[118] or injection of dexamethasone into the lipoatrophic lesions resulted in return of subcutaneous fat tissue in a few reported cases.[119–121]

3.2.4 | Skin manifestations of continuous subcutaneous insulin infusion (CSII) and Continuous Glucose Monitoring (CGM)

Combined use of CSII and CGM requires use of multiple insertion sites with additional risk of skin-related complications. This is an important consideration for younger children who have a smaller surface area available for sites and for long-term pump users.[117]

Poor sterile technique for insertion of insulin infusion sets and the longer use of CSII are associated with microbial colonization and may consequently lead to infections and abscesses, commonly caused by *Staphylococcus aureus* and *Staphylococcus epidermidis*.[122] Skin infections are preventable with regular changing of the infusion set catheter at least every 3 days using sterile technique and good hygiene.[123]

Use of CGM may also associated with problems including skin irritation and difficulties keeping the sensor/transmitter attached, and this may limit successful CGM use in some patients. Skin irritation can be exacerbated by high temperatures and humidity, excessive sweating and contact dermatitis and skin irritation related to CGM adhesive, or other adhesive products, plastic or nickel parts of the sensor, support mount, and/or transmitter.[124] To prevent rashes and dry skin due to the frequent application and removal of sensor adhesive and supplemental adhesive products, patients should be instructed to rotate sensor insertion sites. Moreover, to make sensor removal less

traumatic, adhesive removers may be used to prevent rashes and dry skin, especially in overused areas.[125]

Use of supplemental products to minimize these issues may reduce skin irritation and improve adherence. Transparent dressings and film barrier products can be tried when an allergic reaction to the adhesive or skin irritation from the plastic or metal components of the sensor/transmitter unit is suspected.[117,125] Treatment of eczematous lesions should follow standard guidelines, including use of emollients and topical steroid creams as required.

3.2.5 | Necrobiosis lipoidica (NL) diabeticorum

Necrobiosis lipoidica is a rare chronic granulomatous dermatitis characterized by plaques on the shins of tibia with red-brown edges and atrophic, yellow-brown, telangiectatic centers.[126–128] Although commonly asymptomatic, affected skin may be fragile and painful ulcerations develop in 25% to 33% of cases.[129,130] The pretibial region is the area typically affected and only rarely on hands, fingers, face, and scalp.[131] Patients with type 1 diabetes develop necrobiosis lipoidica at an earlier mean age than those with type 2 and those without diabetes. It appears usually in young or middle adulthood[132]; few cases have been, however, reported in childhood and adolescence.[133–135] It has been suggested that Necrobiosis lipoidica (NL) is one of the possible manifestations of microangiopathy, but the impact of poor glucose control as a causative factor in the development and progression of necrobiosis lipoidica lesion remains controversial with limited data available in the pediatric population.[136]

The treatment of necrobiosis lipoidica is challenging, with initial therapy including topical, intralesional or systemic corticosteroids, but responses vary. Approximately 17% of cases spontaneously remit after 8 to 12 years.[130] Some authors have reported a beneficial effect from smoking cessation and improved blood glucose control.[137]

3.2.6 | Vitiligo

Vitiligo vulgaris, or skin depigmentation, occurs more commonly in type 1 diabetes. From 1% to 7% of all diabetic patients have vitiligo as compared with 0.2% to 1% of the general population.[138] Measurement of 25-hydroxyvitamin D levels and supplementation should be considered, since vitamin D deficiency is common in people with vitiligo.[139] Treatment of vitiligo is often unsatisfactory. Patients should be advised to avoid the sun and to use broad-spectrum sunscreens. For localized vitiligo, topical corticosteroids or calcineurin inhibitor-based creams are preferred, whereas for generalized vitiligo ultraviolet B light treatment may be effective.[140]

3.2.7 | Combined autoimmune conditions: APS and APECED

The co-occurrence of vitiligo and other autoimmune conditions, should raise the diagnostic consideration of APS, as an immune endocrinopathy characterized by the coexistence of at least two endocrine gland insufficiencies.

APS-1, also known as 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 21q22.3.[141,142] APS-2, which is much more common than APS-1 and usually commences later in life than either APS-1 is defined by the combination of at least two of three diseases in the same patient: adrenal insufficiency, type 1 diabetes, and autoimmune thyroid disease. APS-2 may also be associated with IgA deficiency, Graves disease, primary hypothyroidism, hypogonadism, hypopituitarism, Parkinson's disease, myasthenia gravis, celiac disease, vitiligo, alopecia, pernicious anemia, and stiff-man syndrome.[143] APS-2 is usually associated with class II HLA alleles, particularly DRB1*0401 and DRB1*0404.[143] The prevalence of type 1 diabetes is 4% to 20% in APS-1 and 60% in APS-2.[144,145]

APECED is a rare autosomal recessive disease caused by mutations of the AutoImmune REgulator gene. The clinical diagnosis is defined by the presence of at least two components of the classic triad including chronic mucocoutaneous candidiasis, chronic hypoparathyroidism, and AD. Other common features of the disease are hypergonadotropic hypogonadism, alopecia, vitiligo, autoimmune hepatitis, type 1 diabetes, and gastrointestinal dysfunction.[146]

3.2.8 | Psoriasis

The presence of psoriasis is more common in type 1 diabetes patients and is consistent with a common autoimmune predisposition.[147] In a recent study, many of affected patients were postpubertal female, suggesting a role of sex hormones in facilitating this disease onset.[148]

3.2.9 | Other diabetes-related skin conditions

Other diabetes-associated skin conditions include granuloma annular, diabetic dermopathy, acquired perforating dermatosis, and bullosis diabeticorum, or diabetic bulla. There are also other skin disorders that occur more frequently in diabetic individuals like pruritis, xerosis, lichen planus, finger pebbles, and skin tags.[106,149] Hyperglycemia leads to important metabolic and immunological alterations, so that people with diabetes tend to be more susceptible to skin infections.[149]

3.2.10 | Limited joint mobility in childhood diabetes

The cause of limited joint mobility is the deposition of abnormal collagen in the connective tissues around the joints. The condition can occur in both type 1 and type 2 diabetes and is linked to both duration of diabetes and diabetes control. The prevalence also increases with age and smoking.[150–152] The risk of developing limited joint mobility was related to higher HbA1c levels, as well as puberty.[153] Enzymatic and non-enzymatic glycosylation of skin collagen and the production of advanced glycation end products, which lead to abnormal crosslinking and decreased turnover of collagen, are thought to be responsible.[154–156]

Limited joint mobility changes are seen in patients with diabetes begin in the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the little finger and extend radially; and in some, the distal Interphalangeal (IP) joints were involved. Limitation, considered only if bilateral, is also seen in the MCP and larger joints, most commonly the wrist and elbow, but also ankles and cervical and thoracolumbar spine.[157,158] The limitation is painless and non-disabling in most instances; however, severe finger contracture could interfere with certain tasks. Limited joint mobility of the hand may be

demonstrated by having the patient place the hands on a flat surface palm down with the fingers fanned. The entire palmar surface of the fingers should be expected to make contact.[157,158]

3.2.11 | Insulin edema

Insulin edema can develop in relation with insulin therapy, though this complication is rare. Insulin edema commonly occurs shortly after the initiation of intensive insulin therapy in newly diagnosed and poorly controlled patients or following a high-dose insulin therapy among diabetes patients with poor nutrition.[159,160] The true incidence of insulin edema rate is not known and is reported most often among children and adolescents.[159] Despite its self-limiting nature, it is rarely observed with pleural effusion, heart failure, or generalized edema.[161] The etiology may be due to increased capillary permeability caused by chronic hyperglycemia[162] as well as the direct effect of insulin having a direct antinatriuretic effect on the kidney.[163,164] Insulin has been proven to increase vascular permeability in both healthy individuals and diabetes patients.[165] Insulin edema often improves spontaneously in 1 to 3 weeks and decreased insulin doses can also help to reduce edema.[159] Short-term diuretic treatment,[160] salt restriction, and ephedrine[166,167] have been described and may be effective in the treatment of acute edema, but are rarely indicated.

3.2.12 | Bone health and type 1 diabetes

Type 1 diabetes may be associated with osteoporosis and an increased risk of fractures.[168] A recent population-based cohort[169] reported that risk of incident fracture in type 1 diabetes patients was higher across the life span and impacted both sexes equally. In childhood (0-19 years), the increased risk for all fracture types was higher by 14% (range 1%-29%) and is double the rate in type 1 diabetes adults as compared to healthy controls.[169] Despite the higher risk of fracture, abnormal bone density as assessed by dual X-ray absorptiometry (DXA) is not always consistently low in youth and adults with type 1 diabetes, with potential biases including pubertal status, diabetes duration, and differing methods to assess bone mineral density (BMD).[170,171] Identification of potential risk factors impacting fracture rates, that include aberrant metabolic control (HbA1c), dyslipidemia as well as the presence of other microvascular complications have been described in many, but not all reports.[169,172]

Abnormal bone accrual (density and quality) in type 1 diabetes likely has a multifactorial etiology, involving reduced bone formation and abnormal bone quality. Two major determinants of bone strain in children are muscle action 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. This is important, as the mechanisms involved in abnormal BMD in celiac disease may not only be due to potential impaired absorption of calcium and or vitamin D, but also include inflammatory pathways (see section 3.1.3).

In all patients with type 1 diabetes, adequate nutrition including calcium, maintenance of normal vitamin D levels, avoidance of smoking and regular weight-bearing exercise are important for bone health. In addition, screening for vitamin D deficiency, particularly in high-risk groups (celiac disease, autoimmune thyroid disease, darker skin tone) should be considered in young people with type 1 diabetes with consideration of treatment using appropriate guidelines.[173,174]

3.2.13 | Oral health

Young people with type 1 diabetes are at increased risk of oral health problems, including periodontal disease, gingivitis, oral infections, and caries, with a greater risk in those with higher HbA1c.[175–178] High blood glucose levels contribute to reduced salivary flow, which contributes to tooth decay and periodontal bone loss. Treatments for hypoglycemia such as sweetened carbonated beverages and candies may also increase the risk of tooth decay. In adults with type 1 diabetes, suboptimal glycemic control is associated with an increased risk of future tooth loss.[179] Despite the increased risk, there is some evidence that children with diabetes have poor oral hygiene practices.[176] Therefore, as part of preventive care, maintenance of oral health and regular dental review are recommended in young people with type 1 diabetes.

Conflict of interest

The authors have declared no relevant conflicts of interest.

ORCID

Farid H. Mahmud http://orcid.org/0000-0002-3557-3584
Nancy S. Elbarbary http://orcid.org/0000-0001-8713-0657
Mikael Knip http://orcid.org/0000-0003-0474-0033
Maria E. Craig http://orcid.org/0000-0001-6004-576X

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