

# ISPAD Clinical Practice Consensus Guidelines 2022: Other complications and associated conditions in children and adolescents with type 1 diabetes

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## 1 | WHAT IS NEW OR DIFFERENT

- Revised recommendations for celiac disease (CD) screening and biopsy that include consideration of a serology-based diagnostic approach.
- Expanded section on skin disorders that includes continuous glucose monitoring (CGM)-related and insulin pump-related skin issues.
- Updated section on bone health with general recommendations regarding optimization of bone health in youth with type 1 diabetes (T1D).

• Screening for thyroid disease by measurement of TSH, anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies is recommended soon after diagnosis of diabetes once the individual is clinically stable. **B**

Thereafter, TSH should be measured every second year in asymptomatic individuals and every year in individuals with positive antibodies at diagnosis or a family history of autoimmune thyroid disease. **E** TSH should be measured sooner with the presence of clinical signs or symptoms of thyroid disease, including goiter or growth impairment. **E**

- CD may present with varied clinical signs and symptoms that may be gastrointestinal (diarrhea, nausea, abdominal pain), extra intestinal (unexplained weight loss, iron deficiency anemia, decreased bone mineralization, aphthous stomatitis) or diabetes-related (unexplained hypoglycemia). The process of active case finding on the basis of symptoms can be challenging as CD is frequently asymptomatic in children and young adults with T1D. **B**
  - Screening for CD is recommended during the initial year of diabetes diagnosis and at 2–5 years intervals. **C**

## 2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Regular monitoring of anthropometric measurements and physical development, using growth and body mass index (BMI) standards, are essential in the continuous care of children and adolescents with T1D. **E**

More frequent assessment is indicated if the clinical situation suggests the possibility of symptomatic CD or the child has a first-degree relative with CD. Clinical signs and symptoms of CD or the availability of blood testing for other reasons may necessitate screening for CD at the time of diabetes diagnosis, but clinicians should consider the potential challenges for children and families in managing new onset diabetes plus CD in asymptomatic cases and defer screening after the period of initial diagnosis. **E**

- Measurement of human leukocyte antigen (HLA)-DQ2 and DQ8 is rarely helpful to exclude CD in individuals with T1D and is not recommended as a screening test. **B**
- Screening for IgA deficiency should be performed at the time of CD screening. In individuals with diabetes with confirmed IgA deficiency (low total IgA concentrations), screening for CD should be performed using an IgG-based specific antibody tests (tissue transglutaminase (TTG-IgG) or endomysial antibody (EmA-IgG) or both). **B**  
 All IgA deficient individual with diabetes who are positive for an IgG-based serological test should be referred to a pediatric gastroenterologist for biopsy. **C**
- In children with normal IgA levels, use of TTG-IgA as an initial screening test, with levels exceeding  $\geq 10$  times the upper limit of the TTG-IgA assay with confirmation of positive EmA-IgA in a second blood sample while on a diet containing gluten can be used to diagnose CD, as suggested by recent European guidelines. Only antibody tests with calibrator curve-based calculation and having the TTG-IgA  $\geq 10$  times the upper limit value within their measurement range, should be used. It is recognized that this approach has not been universally adopted as standard of care internationally. **E**
- In the symptomatic child, a biopsy-sparing approach may be considered on a case-by-case basis in consultation with a pediatric gastroenterologist and the child and family with initiation of a gluten-free diet with resolution of symptoms. **E**
- In the asymptomatic child, evidence for a biopsy-sparing approach is limited in children with T1D and was not addressed by recent European guidelines. The implications of a life-long commitment to be on a gluten-free diet in an individual with both CD and diabetes without symptoms is an important consideration and the decision to perform duodenal biopsies for confirmation of gastrointestinal pathology should also be discussed with parents and the child. **E**
- Upon confirmation of the diagnosis of CD, they should receive educational support from an experienced pediatric dietitian with knowledge of the gluten-free diet (GFD) and both individuals with diabetes and their diabetes care team should be vigilant as insulin requirements may change during transition to the GFD. **E**
- Children with CD should have annual screening for thyroid function and monitoring of vitamin D to optimize bone health. **E**
- Diabetes care providers should be alert for symptoms and signs of other autoimmune diseases in children and adolescents with T1D

including Addison's disease, autoimmune gastritis, juvenile idiopathic arthritis (JIA), other gastrointestinal diseases (e.g., Crohn's disease, ulcerative colitis, autoimmune hepatitis), although these are rare. **E**

Individuals with T1D and adrenal disease might have a greater risk of mortality; therefore, these individuals require additional vigilance to optimize metabolic outcomes, to reduce hypoglycemia and diabetic ketoacidosis and to prevent adrenal crises. **E**

- Routine clinical examination should be undertaken for skin and joint changes. Regular screening by laboratory or radiological methods is not recommended. **E**  
 Education regarding proper injection technique, rotation of injection sites with each injection and non-reuse of needles remains the best strategies to prevent lipohypertrophy (LH) and lipoatrophy (LA).  
  - Injection sites should be regularly assessed at each clinic visit for LH and LA as they are potential causes of glucose variability. **C**
  - Routine clinical examination for skin irritation should be performed in children and adolescents using insulin pumps and/or CGM. Rotation of pump and sensor insertion sites is recommended. **E**
- Screening for vitamin D deficiency, particularly in high-risk groups (CD, darker skin pigmentation) should be considered in young people with T1D and treated using appropriate guidelines. **E**
- Impaired bone health is an emerging long-term complication of T1D. Individuals with diabetes should be counselled to optimize calcium and vitamin D intake, avoid smoking, and perform regular weight-bearing exercise. Individualized assessments of bone health may be considered in children with medical co-morbidities such as CD or a family history of early osteoporosis. **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 (Table 1).

Larger body size and rapid growth, with greater height velocity, prior to and at diagnosis of T1D has been reported.<sup>1–5</sup> The precise mechanism for this and whether or not this increased height is maintained is unclear; however, factors in children who are autoantibody positive, a sustained increased BMI is associated with an increased risk of progression to T1D<sup>6,7</sup> and high BMI has been identified as a risk factor for islet autoimmunity and subsequent development of T1D<sup>8,9</sup>; however not all reports confirm this.<sup>10</sup>

There is considerable evidence that youth with suboptimal glycemic management show a decrease in height velocity, whilst better-managed youth with diabetes maintain normal rates of growth.<sup>11</sup> Insulin is a major regulator of the growth hormone (GH) and insulin like growth factor-1 (IGF-1) axis; adequate insulin secretion and

normal portal insulin concentrations are needed to maintain normal serum concentrations of IGF-1 and insulin like growth factor binding proteins, and to promote growth.<sup>12,13</sup> 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/IGF-1 concentrations and height outcomes, independent of glycemic status.<sup>12</sup> The negative effect of elevated HbA1c on growth appears to be exacerbated during puberty, a time of physiological insulin resistance.<sup>14</sup> Significant impairment in growth during puberty has also been reported particularly in young people who develop albuminuria.<sup>15</sup> In most youth with T1D, modern diabetes management using insulin pump or >3 injections daily is associated with normal growth.<sup>16,17</sup> 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; however new cases continue to be reported.<sup>18,19</sup> Insulin insufficiency, CD and other gastrointestinal disorders should also be considered in these cases. Recently, a mutation in an enzyme involved in glycogen metabolism (catalytic subunit of glycogen phosphorylase kinase) was reported in a case of Mauriac syndrome that increased glycogen deposition in the liver. The postulated mechanism is that this mutant enzyme combines with hyperglycemia to directly inhibit glycogen phosphorylase activity, resulting in many of the phenotypic features observed in this syndrome.<sup>20</sup>

Once the child or adolescent has regained weight after the initial diagnosis of T1D, excessive weight gain may indicate high-energy intake, which may be related to excessive exogenous insulin. Excessive weight gain is more common during and after puberty, especially in girls, as well as in those whose diabetes was diagnosed during puberty.<sup>21</sup> Historically, The Diabetes Control and Complications Trial and other studies reported increased weight gain as a side effect of improved glycemic management with intensive insulin therapy, potentially related to the impact of recurrent hypoglycemia.<sup>21,22</sup> Children with obesity and T1D have a higher prevalence of cardiovascular risk factors (hypertension, dyslipidemia and cardiac autonomic dysfunction) than normal weight children with T1D.<sup>23,24</sup> Recent data from multiple international registries show higher rates of overweight and obesity in children and adolescents with T1D, compared to their peers without diabetes.

Therefore, careful monitoring based on BMI-charts for age and gender and management of weight gain should be emphasized in diabetes care as obesity is a modifiable cardiovascular risk factor.<sup>25-27</sup> There is a complex interplay among age, puberty, insulin requirement, metabolic status and BMI.<sup>28</sup> Use of adjunctive therapy with insulin sensitizing agents, such as the addition of metformin along with insulin does not improve glycemic outcomes in overweight adolescents with T1D; however, it may lead to decreased insulin requirements and a reduction of BMI.<sup>29</sup>

Girls with T1D are at increased risk of being overweight<sup>21</sup> and clinicians must also be aware that these weight changes are recognized risk factor for later development of eating disorders.<sup>30-32</sup> In association with increased weight, there is also the risk of ovarian

hyperandrogenism, hirsutism and polycystic ovarian syndrome in girls with T1D.<sup>33,34</sup> In a recent study of adolescents with hyperandrogenism and T1D, metformin treatment significantly decreased serum androgen concentrations compared to placebo but did not significantly affect clinical parameters, such as hirsutism, ovulation and glycemic status. Therapy for only 9 months, however, is generally thought to be insufficient to impact hirsutism.<sup>35,36</sup> Increased doses of insulin are usually required during puberty and it is important to reduce insulin doses after pubertal development is completed and insulin resistance has decreased.

Risk of delayed menarche and menstrual irregularities together with hyperandrogenism are increased in youth who develop T1D before the onset of puberty, and several studies indicate that the delay is independent of glycemic management.<sup>37-39</sup> A recent study indicated delayed menarche and earlier menopause in females with T1D resulting in a shorter reproductive period in females with T1D, which may affect reproductive health and requires additional research.<sup>40</sup>

## 4 | ASSOCIATED AUTOIMMUNE CONDITIONS

Children with T1D are at increased risk for comorbid autoimmune diseases and clinicians must be aware of the symptoms and risk factors associated with common comorbid autoimmune diseases. A high proportion of children and adolescents with T1D have detectable organ-specific autoantibodies (e.g., thyroid, CD) in addition to islet autoantibodies, and approximately 25% of individuals with T1D are diagnosed with another autoimmune disease.<sup>41-44</sup> Comorbid autoimmune diseases occur more commonly in females compared to males and the incidence increases with age.<sup>41</sup> In situations where laboratory testing is not available or is cost prohibitive, the clinician must rely on careful monitoring of linear growth and relevant symptoms. Screening at regular intervals for common comorbid conditions (autoimmune thyroid disease [AITD] and CD), which may be subclinical or asymptomatic, allows for earlier identification and treatment.

Autoimmune thyroid disease (AITD) is the most common comorbid autoimmune condition seen in T1D followed by CD.<sup>41</sup> Other autoimmune conditions that occur less commonly in youth with T1D include primary adrenal insufficiency, collagen vascular disease (e.g., rheumatoid arthritis, lupus erythematosus, psoriasis, scleroderma), other gastrointestinal diseases (e.g., Crohn's disease, ulcerative colitis, autoimmune hepatitis, autoimmune gastritis), and skin diseases (e.g., vitiligo, scleroderma). Rare cases of multiple sclerosis have been reported in association with T1D in childhood and adolescence and will not be described in detail.<sup>45,46</sup>

### 4.1 | Hypothyroidism/Hashimoto thyroiditis

Thyroid disease occurs more frequently in children and adults with T1D than in the general population. The incidence of AITD in children and adolescents ranges from 0.3 to 1.1 per 100 patient years and prevalence is approximately 3%-8% of children with T1D.<sup>47,48</sup> The

prevalence of AITD increases with age to approximately 20%; most have hypothyroidism.<sup>41</sup> Anti-thyroid antibodies can be detected in up to 29% of individuals soon after diagnosis with T1D and are strongly predictive for the development for AITD, mostly hypothyroidism.<sup>42,48,49</sup> Anti-thyroid antibodies are observed more frequently in girls than in boys and are associated with age, diabetes duration and pubertal maturity.<sup>50</sup> In addition, the presence of islet autoantibodies to GAD (Glutamic Acid Decarboxylase) and ZnT8 (Zinc Transporter-8) are associated with thyroid autoimmunity.<sup>43,51</sup> Screening children for anti-thyroid antibodies (antithyroid peroxidase and antithyroglobulin) can help stratify which youth with diabetes 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 management may not be significantly affected, but hypoglycemia has been linked to hypothyroidism.<sup>52</sup>

Overt 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 (euthyroid sick syndrome) if an individual with diabetes is not metabolically stable (e.g., after diabetic ketoacidosis) or has suboptimal blood glucose management.<sup>53,54</sup> In thyroid autoantibody positive, asymptomatic individuals, compensated (subclinical) hypothyroidism may also be observed, with normal free T4 and mildly increased TSH levels.

Treatment of hypothyroidism in T1D 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 levels, management of treated thyroid disease should include measurement of thyroid function tests after changing levothyroxine dosage. It is important to note that untreated hypothyroidism can worsen total cholesterol, LDL cholesterol and triglyceride levels.<sup>55</sup> Children should also have their thyroid gland palpated yearly for the development of nodules or cysts that would require further evaluation.

## 4.2 | Hyperthyroidism

Hyperthyroidism is less common than hypothyroidism in association with T1D, 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.<sup>41,48,56,57</sup> Hyperthyroidism may be due to Graves' disease or the hyperthyroid phase of Hashimoto's thyroiditis, sometimes referred to as Hashitoxicosis.

Hyperthyroidism is characterized by weight loss, increase in appetite, palpitations, tachycardia, tremors, hyperactivity, 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.<sup>58</sup> Hyperthyroidism is confirmed with a suppressed TSH level 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 anti-thyroid drug carbimazole or methimazole; which is the recommended treatment in children due to the increased risk of liver failure with propylthiouracil treatment.<sup>59</sup> Beta-adrenergic blocking drugs are helpful during the acute phase of thyrotoxicosis to manage tachycardia and agitation. If people with diabetes do not go into remission or cannot be managed on antithyroid medications, definitive treatment options include thyroidectomy or ablation with radioactive iodine.<sup>60</sup>

## 4.3 | Celiac disease

The prevalence of CD ranges from 1%–16.4% among children and adolescents with T1D.<sup>61–64</sup> An international comparison study that included 53,000 children and adolescents with T1D across three continents reported a prevalence of biopsy proven CD of 3.5%, with rates ranging from 1.9% in the U.S. to 7.7% in Australia.<sup>61</sup> A recent report of the SWEET registry reported a mean prevalence of 4.5% with rates ranging from 1.9% in Asia/Middle East to 6.9% in Australia/New Zealand<sup>64</sup>; however these data may not be fully reflective of high rates of CD from other clinic- and population-based studies showing high rates of CD in the Middle East and Indian subcontinent.<sup>65,66</sup>

The risk of CD 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.<sup>62,67–69</sup> This association is common to both genders. The prevalence of CD increases with longer duration of diabetes.<sup>63</sup>

Most cases of CD are diagnosed within the first year after T1D diagnosis and youth with T1D may develop CD within the first 5–10 years after T1D diagnosis. However, it is important to appreciate that the diagnosis of CD can also be made beyond this period into adulthood.<sup>64–66,70,71</sup> While there may be pragmatic reasons to assess for CD at diagnosis to coincide with blood testing, consideration of CD screening in asymptomatic children may be deferred after the period of initial diagnosis, as managing both new onset diabetes and CD may be overwhelming for children and their families.

CD is often asymptomatic; i.e., not associated with gastrointestinal symptoms, poor growth and/or deterioration in glycemic status or hypoglycemia.<sup>72–76</sup> The presence of CD 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), extra intestinal symptoms (including iron deficiency anemia, unexplained poor growth, weight loss, recurrent aphthous ulceration, decreased bone mineralization) or unexplained hypoglycemia.<sup>68</sup> It should be noted that tissue transglutaminase IgA (TTG-IgA) antibodies titers are higher in people with diabetes with gastrointestinal manifestations as compared to asymptomatic individuals.<sup>77</sup>

Screening for CD is based on the detection of IgA antibodies (TTG-IgA and/or EmA-IgA); both tests demonstrate sensitivity and specificity >90%.<sup>78,79</sup> TTG thresholds extrapolated from the general population for the diagnostic evaluation of CD may not be suitable for use in asymptomatic individuals with T1D. Higher thresholds than the

manufacturer's recommendations have been reported in individuals with asymptomatic CD.<sup>79</sup> Laboratories reporting CD-specific antibody test results for diagnostic use should continuously participate in quality control programs on a national or international level. The approach to use HLA-DQ2 and HLA-DQ8 as first line screening, because CD is unlikely if both haplotypes are negative, is not recommended, given the high proportion of individuals with diabetes who carry these risk alleles. Thus, the use of HLA as first line testing to screen for CD in this population is neither practical nor cost effective.<sup>80–84</sup>

IgA deficiency, 1:500 in the general population, is more common in people with T1D and those with CD.<sup>85</sup> Therefore, screening for IgA deficiency should be performed at the time of CD screening. If the child is IgA deficient, IgG-specific antibody tests (TTG IgG, EmA IgG) must be used for screening. This is important because CD may be more common in those with IgA deficiency than in the general population.<sup>86</sup> All individuals with diabetes who are IgA deficient and positive for an IgG based serological test should be referred to a pediatric gastroenterologist for biopsy.

In children with normal IgA levels, recent European guidelines suggest use of TTG-IgA as an initial screening test. Levels exceeding  $\geq 10$  times the upper limit of normal (ULN) for the TTG-IgA assay, with confirmation of positive EmA IgA in a second blood sample while on a diet containing gluten can be used to diagnose CD.<sup>80</sup> Only antibody tests with calibrator curve-based calculation, and having the TTG-IgA  $\geq 10$  times ULN value within their measurement range, should be used. This approach has not been universally adopted as standard of care internationally and is inconsistent with other guidelines.<sup>87</sup>

In people with diabetes with positive TTG-IgA  $< 10 \times$  ULN a small bowel biopsy with at least 4 biopsies from the distal duodenum and at least 1 from the bulb should be taken<sup>80</sup> to confirm the diagnosis of CD by demonstrating subtotal villus atrophy, as outlined in the Marsh classification.<sup>88</sup> Several biopsy samples should be taken, as CD 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.<sup>89,90</sup>

In the symptomatic child, a biopsy-sparing approach may be considered on a case-by-case basis in consultation with a pediatric gastroenterologist and the child and family. Initiation of a gluten-free diet (GFD) and resolution of symptoms serves as indirect evidence of the diagnosis.

In the asymptomatic child, evidence for a biopsy-sparing approach is limited in children with T1D and was not addressed by recent European guidelines.<sup>80</sup> The implications of a life-long commitment to be on a GFD in an individual with both CD and diabetes without symptoms is an important consideration and the decision to perform duodenal biopsies for confirmation of gastrointestinal pathology should be discussed with parents and the child.

There are challenges to broader implementation of assay cutoffs for diagnostic purposes that include a lack of international standardization, assay variability, as well as CD and diabetes related factors.<sup>91,92</sup> For example, TTG-IgA positivity at the time of screening may be transient and there are several reports of spontaneous normalization of CD antibodies<sup>93,94</sup> emphasizing serological follow-up

(in 3–6 months) instead of immediate recourse to duodenal biopsy and the need for a duodenal biopsy to verify the diagnosis, especially in asymptomatic individuals with diabetes.<sup>95</sup>

Children with coexisting T1D and CD have been observed to have low HDL-cholesterol and increased LDL-cholesterol, significantly higher rates of concomitant autoimmune thyroid disease, and an increased risk for depression and disordered eating behaviors. These associations indicate that children and adolescents with both conditions should have regular assessments of their serum lipid profiles, annual screening of thyroid function, and regular screening for depression and eating disorders.<sup>96–98</sup>

A GFD normalizes the bowel mucosa, frequently leads to disappearance of antibodies, and has an impact on the normalization of lipid profile,<sup>99,100</sup> but may not necessarily impact glycemic management.<sup>68,74,101</sup> There is a report, that GFD is associated with greater glycemic excursions and inadequate nutritional intake in youth with T1D and CD; therefore, clinical management should also address glycemic variability and dietary quality and both people with diabetes and their diabetes care team should be vigilant as insulin requirements may change during transition to the GFD.<sup>102,103</sup> The aims of the GFD include reduction of the possible risk of gastrointestinal malignancy and the effects of subclinical malabsorption that may include osteoporosis, iron deficiency, and growth failure.<sup>68,104,105</sup> Long-standing CD in the context of T1D may be associated with an increased risk of retinopathy,<sup>106</sup> and the increase the risk of albuminuria is increased in those not maintaining a GFD.<sup>107,108</sup> There are also reports of increased risk for microvascular and potentially for macrovascular complications in T1D youth with comorbid CD.<sup>108–110</sup>

An important consideration for children and their families relates to the lifestyle impact because of transition to a GFD, especially in the context of diabetes. Children diagnosed with CD should receive education and support from an experienced pediatric dietitian knowledgeable about the GFD. Educational materials for youth with diabetes and families should be made available, that address both dietary issues and adaptation to a GFD in home, school and social settings.<sup>111</sup> Online education for GFD teaching is a helpful tool in teaching families with T1D and CD.<sup>112</sup>

Suboptimal maintenance of a GFD may be associated with reduced quality of life, worse glycemic management, and lower height SDS.<sup>100,113</sup> Diabetes-related factors such as HbA1c and symptoms are also important contributors to lower QOL in T1D youth with both conditions.<sup>114</sup>

The prevalence of CD is increased among first-degree relatives of children with T1D, and consequently family members of a child with newly diagnosed CD should also be screened.<sup>95</sup>

#### 4.4 | Primary adrenal insufficiency (Addison's disease)

Up to 2% of people with T1D have detectable anti-adrenal autoantibodies.<sup>42,115,116</sup> The HLA DRB1\*04-DQB1\*0302 (primarily DRB1\*0404) and DRB1\*0301-DQB1\*0201 haplotypes define subjects at high-risk for

adrenal autoimmunity,<sup>117</sup> while homozygosity for the MHC (HLA) class I chain-related gene A (MICA) polymorphism 5.1 defines those at highest risk for progression to overt Addison's disease.<sup>118</sup> A person with T1D who has the DRB\*0404 allele and 21-hydroxylase antibodies has a 100-fold risk of developing Addison's disease. Adrenal insufficiency may be associated with T1D as part of the autoimmune polyglandular syndromes (APS-1 and APS-2).<sup>119</sup> 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 (FOXP3) gene, which encodes a transcription factor the development and function of regulatory T cells.<sup>120,121</sup>

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 as well as severe or recurrent infections.<sup>122</sup> The diagnosis is confirmed by demonstrating a low serum cortisol response to an ACTH stimulation test and positive anti-adrenal (21-hydroxylase) antibodies. Treatment is urgent and lifelong, consisting of glucocorticoid and mineralocorticoid (fludrocortisone) replacement. In asymptomatic children with positive adrenal antibodies, a rising plasma ACTH level suggests a failing adrenal cortex and the development of primary adrenal insufficiency. Longer-term data have shown a 4-fold greater risk of mortality in youth with both diabetes and adrenal disease, as compared with diabetes alone.<sup>123</sup> These individuals with diabetes require additional vigilance to balance the challenges of diabetes care, optimize metabolic outcomes, and reduce risks of hypoglycemia and diabetic ketoacidosis, and appropriate management and prevention of adrenal crises.<sup>124</sup> It is important to prevent adrenal crises through education, emergency cards, and adjustment of glucocorticoid treatment (stress dose glucocorticoids) in case of intercurrent medical illness, trauma, surgery, or invasive procedures, as well as to identify and treat adrenal crises in a timely manner.<sup>124</sup>

## 4.5 | Autoimmune gastritis

Parietal cell antibodies (PCA) are the principal immunological markers of autoimmune gastritis and react against the H<sup>+</sup>/K<sup>+</sup> ATPase of the gastric parietal cells.<sup>116,125</sup> Chronic damage to the proton pump may result in hypo- or achlorhydria, hypergastrinemia, and iron deficiency anemia due to decreased gastric secretion and decreased iron absorption.<sup>126</sup> PCA may also inhibit intrinsic factor secretion, leading to vitamin B12 deficiency and pernicious anemia.<sup>127</sup> T1D is associated with an increased risk of parietal cell antibody positivity,<sup>128</sup> with prevalence rates in children ranging from 5.3% to 7.5%.<sup>129–131</sup> Physicians should be aware of the possibility of PCA in children and adolescents with T1D in cases of unclear anemia (microcytic as well as macrocytic) or gastrointestinal symptoms, but routine screening is not recommended. In youth with diabetes with positive PCA, blood count, iron

status, and vitamin B12 status should be assessed. If the individual with diabetes with positive PCA has gastrointestinal symptoms, a gastroscopy should be considered.

## 4.6 | T1D and systemic autoimmune diseases

In addition to organ-specific autoimmune diseases, other non-organ-specific, or systemic autoimmune diseases, such as JIA, Sjögren syndrome, psoriasis, and sarcoidosis may also develop in individuals with T1D.<sup>132</sup> In children with T1D, JIA is the most frequently encountered non-organ-specific autoimmune condition.<sup>132</sup> The disease affects girls twice as often as boys. There is growing evidence for the common genetic background of JIA and T1D, which is associated with a mutation in the PTPN22 gene encoding an enzyme inhibiting the T-cell activation pathway.<sup>133</sup> Sjögren's syndrome is a systemic autoimmune disease that mostly affects lacrimal and salivary glands. The spectrum of the disease ranges from dryness syndrome to systemic disease of exocrine glands. There are single case reports of T1D occurring in individuals with Sjögren's syndrome.<sup>134</sup>

## 4.7 | Combined autoimmune conditions: APS and APECED

The co-occurrence of vitiligo and other autoimmune conditions should raise the diagnostic consideration of APS, an immune endocrinopathy characterized by the coexistence of at least two endocrine gland insufficiencies. APS-1, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a rare autosomal recessive disease that 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.<sup>135,136</sup> The clinical diagnosis is defined by the presence of at least two components of the classic triad including chronic mucocutaneous candidiasis, chronic hypoparathyroidism, and adrenal insufficiency. Other common features of the disease are hypergonadotropic hypogonadism, alopecia, vitiligo, autoimmune hepatitis, T1D, and gastrointestinal dysfunction.<sup>137</sup> APS-2, which is much more common than APS-1 and usually commences later in life than APS-1, is defined by the combination of at least two of three diseases in the same individual: autoimmune adrenal insufficiency, T1D, and autoimmune thyroid disease. APS-2 may also be associated with IgA deficiency, Graves' disease, primary hypothyroidism, hypogonadism, hypopituitarism, Parkinson's disease, myasthenia gravis, CD, vitiligo, alopecia, pernicious anemia, and Stiff-man syndrome. APS-2 is usually associated with class II HLA alleles, particularly DRB1\*0401 and DRB1\*0404.<sup>120</sup> The prevalence of T1D is 4% to 20% in APS-1 and 60% in APS-2.<sup>138,139</sup> Approximately 3% to 8% of individuals with diabetes or autoimmune thyroid disease have CD.<sup>140</sup> The female-to-male predominance of youth with T1D and thyroid disease is much greater (6.4:1) than the ratio for youth with diabetes alone (1:1).

## 5 | T1D RELATED SKIN CONDITIONS

### 5.1 | Skin problems related to diabetes therapy and chronic devices use

#### 5.1.1 | Insulin-induced lipodystrophy (lipohypertrophy and lipoatrophy)

Insulin-induced lipodystrophy remains an important complication in the care of diabetes. LH and LA are well-recognized dermatological complications of subcutaneous insulin administration.<sup>141</sup> It is important for physicians to be aware of and recognize these insulin-related skin complications.<sup>142</sup>

##### Lipohypertrophy

LH is a frequent complication of insulin therapy characterized by painless induration and swelling caused by fibrous and poorly vascularized lesions in the subcutaneous adipose tissue confined to frequently used insulin injection sites.<sup>143</sup> A recent study showed higher levels of proinflammatory cytokines and anti-insulin antibody are associated with lipodystrophy in T1D.<sup>144</sup> Etiologic factors include tissue trauma caused by substandard injection technique, insufficient injection site rotation, repeated injections into a small area, and reuse or excessive length of the needles. Insulin also has a direct anabolic effect on local skin leading to fat and protein synthesis that is a contributing factor in the pathogenesis of LH.<sup>145</sup> As lipohypertrophic areas are relatively painless, youth with diabetes often continue to use the same area rather than move to a new, more sensitive site. Initial skin changes can be subtle and manifest only as thickening of skin. This can be easily missed by visual inspection and palpation of the skin in areas used for injection is recommended to appreciate the soft, lipoma-like nodules.<sup>146</sup> There are important consequences of LH including suboptimal glucose management and glycemic variability that may increase the risk of diabetes complications.<sup>147</sup> In addition, LH is associated with increased insulin doses by up to 25% due to reduced insulin absorption and variable glycemic excursions related to alterations in the duration of insulin action.<sup>148</sup> In one study, people with diabetes with LH were found to have a 7-times higher risk of unpredictable unexplained hypoglycemia than those without LH.<sup>142</sup> LH can be prevented by adhering to proper insulin injection technique, including regular injection site rotation and limited insulin needle reuse.<sup>149</sup> Needles should be as short as possible to minimize tissue trauma and avoid inadvertent intramuscular administration, especially in thin individuals.<sup>150</sup> Four mm needles are associated with the least risk of causing tissue trauma and inadvertent intramuscular injection; however, choice of needle size must be individualized.<sup>151</sup> Ultrasound has been used to evaluate insulin-induced LH.<sup>152</sup> The method is more sensitive than palpation; ultrasound verified LH was detected in more than 80% of cases. In individuals with diabetes with significant, widespread LH, ultrasound can be used to find suitable sites for injections (“ultrasound injection map”). In practice, physical examination of injection sites for the presence of LH is a key component in the care of children with T1D. Individuals with diabetes should also be taught to examine their own injection sites and how to detect LH.<sup>153</sup>

##### Lipoatrophy

LA is a form of localized lipodystrophy characterized by localized loss of subcutaneous adipose tissue at the site of insulin injection. It 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% with the increasing use of purified insulin.<sup>154,155</sup>

The mechanism of LA is poorly understood; an immune pathogenesis seems likely, and it is seen more often in individuals with diabetes who have other evidence of autoimmunity.<sup>156</sup> Other theories of causation include 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.<sup>157</sup> Repeated use of the same insulin injection site and multiple usage of the same pen needle increases the risk of LA.<sup>158</sup>

Treatment options are limited and include changing the site of injection or infusion cannula and switching insulin analogues<sup>159</sup>; however, this does not always lead to complete resolution of lesions.<sup>160,161</sup> Treatment with steroids, given orally (daily low dose prednisolone)<sup>160</sup> or injection of dexamethasone<sup>161</sup> and cromolyn sodium<sup>155</sup> into the lipoatrophic lesions has been reported to be successful in anecdotal cases.<sup>162,163</sup>

#### 5.1.2 | Dermatological manifestations of diabetes technology devices: Continuous subcutaneous insulin infusion and continuous glucose monitoring

CSII and CGM devices are widely used in youth with T1D as standard therapy or as part of a closed-loop-system as they may improve glycemic management and enhance treatment flexibility.<sup>164</sup> With increasing popularity, a wide range of reported skin reactions and dermatological complications to CSII and CGM devices are frequently reported. Additional CGM and CSII specific skin concerns are described in ISPAD 2022 Consensus Guidelines Chapter 16 Diabetes Technologies: Glucose monitoring and Chapter 17 on Diabetes Technologies: Insulin delivery.

The frequency of reported skin reactions among pediatric CGM users has significant individual variation and skin issues have been reported to be as high as 39%,<sup>165-167</sup> which may affect management and be a barrier to consistent long-term use. A recent systematic review of cutaneous complications in CGM users from clinical trial data reported erythema (55%), pruritus (11%), and induration (9%).<sup>168</sup> Among those using insulin pumps, localized eczematous reactions at the site of infusion set insertion were noted in 14% of youth in one study<sup>169</sup> and a survey of 143 youth documented that nearly half of the cohort reported non-specific eczema.<sup>170</sup>

A history of atopy and the type of adhesive used in a device plays a key role in development of allergic contact dermatitis. Acrylate monomers, that include ethyl cyanoacrylates as well as isobornyl acrylate (IBOA), are common components in the preparation of adhesives, which are known to be a potent source of contact dermatitis.<sup>171,172</sup> In addition, contact dermatitis can occur on the manufacturer adhesives to colophonium and N, N-dimethylacrylamide.<sup>172-174</sup> Acquired

leukoderma (localized areas of depigmentation), have been described with direct skin contact and has been linked to the depigmenting substance hydroquinone monomethyl ether (HMME).<sup>175</sup> There is a need for manufacturing changes to improve breathability and reduce trapped moisture that contribute to skin reactions with the current technologies.<sup>176</sup> Initiatives for full and accurate labelling of the chemical composition of devices were recently presented.<sup>177</sup>

Scarring is another potential dermatological complication from CGM and CSII and appears to be more common in CSII. Scarring manifests as small hypo- or hyperpigmented lesions of fibrous tissue. Although it is unclear whether scarring affects sensor accuracy or insulin absorption, it may disrupt the insertion process of sensors or cannulas, and scarred areas should therefore be avoided.<sup>157,178</sup>

CSII can lead to lipodystrophy, whereas LA is less common than LH.<sup>158,161</sup> CGM use is not thought to contribute to lipodystrophy and a study indicated that CGM accuracy is not compromised in LH.<sup>179</sup>

The prevention of these skin-related complications includes good nutrition, hydration, site rotation, correct device placement, proper removal technique, and prophylactic skin care for optimal skin integrity.<sup>180</sup> Skin preparation should include exfoliation, trimming hair, and removing oil before adhesive placement to maximize adhesion and minimize irritation. Key steps include appropriately cleaning the skin and drying it completely before attempting to place CGM sensors and CSII catheters, and use adhesive barriers, tackifying agents or possibly off-label steroid sprays (e.g., fluticasone) prior to insertion for those with known prior reactions.<sup>181</sup> Sweating could be mitigated by applying antiperspirant to the skin before insertion.<sup>182</sup> Removal of adhesives by including use of removal agents may also be used to minimize tissue damage. Moreover, individuals with diabetes should be taught to monitor sites for pain, edema, erythema, warmth, or suppuration.

### 5.1.3 | Insulin edema

Insulin edema is a complication of insulin therapy that may occur shortly after the initiation of intensive insulin therapy in newly diagnosed with suboptimal glycemic management<sup>183</sup> or following high dose insulin therapy in poorly nourished individuals with diabetes.<sup>184,185</sup> The true incidence of insulin edema is not known and insulin edema is reported most often among children and adolescents.<sup>184</sup> Despite its self-limiting nature, it is rarely observed with pleural effusion, heart failure, or generalized edema.<sup>186</sup> The mechanisms resulting in insulin edema is the deficiency of insulin, which results in a catabolic state.<sup>187,188</sup> Intensive fluid resuscitation during the initial phase of treatment may lead to extravasation of fluid into the subcutaneous tissue, exacerbating edema.<sup>189</sup>

Moreover, the severity of edema negatively correlates with BMI, with the most severe cases occurring in the severely underweight individuals with diabetes, further suggesting a link between the resolution of the catabolic state upon the commencement of insulin and the development of edema.<sup>189</sup>

Insulin edema often improves spontaneously in 1 to 3 weeks and decreased insulin doses can also help to reduce edema.<sup>184</sup> Short-term

diuretic treatment,<sup>185</sup> salt restriction, and ephedrine<sup>190</sup> have been described and may be effective in the treatment of acute edema, but are rarely indicated. The resumption of insulin necessary for the management of T1D should be gradual and accompanied by a frequent reassessment of fluid status.<sup>191,192</sup>

## 5.2 | Dermatological conditions associated with diabetes

### 5.2.1 | Necrobiosis lipoidica diabetorum

Necrobiosis lipoidica is an uncommon chronic granulomatous dermatitis characterized by plaques on the shins of tibia with red-brown edges and atrophic, yellow-brown, telangiectatic centers.<sup>193,194</sup> The prevalence of NL ranges from 0.3% to 1.2% among youth with diabetes mellitus,<sup>195</sup> of which two-thirds have T1D. NL is generally asymptomatic unless it is ulcerated and painful in 25% to 33% of cases.<sup>196</sup> NL is more common in females than in males.<sup>197</sup>

NL usually appears during young and middle adulthood,<sup>198</sup> although there are a few studies reporting cases in childhood and adolescents.<sup>199,200</sup> The pretibial region is the area typically affected and only lesions rarely occur on hands, fingers, face, forearms, and scalp<sup>197</sup> and, recently reported, also on the trunk.<sup>201</sup> It has been suggested that NL is possibly a manifestation of microangiopathy, but the impact of suboptimal glucose management as a causative factor in the development and progression of NL lesion remains controversial and there are limited data available in the pediatric population.<sup>202</sup>

The treatment of NL is challenging; initial therapy includes topical, intralesional or systemic corticosteroids, but responses vary. Approximately 17% of cases spontaneously remit after 8 to 12 years.<sup>203</sup> Some authors have reported a beneficial effect from smoking cessation and improved blood glucose management.<sup>204</sup> In case reports, doxycycline,<sup>205</sup> anti-TNF $\alpha$  agents,<sup>206</sup> JAK1/2 inhibitor<sup>207</sup> showed promising results in the management of this condition.

### 5.2.2 | Vitiligo

Vitiligo vulgaris, or skin depigmentation, occurs more commonly in T1D; 1% to 7% of all individuals with diabetes have vitiligo compared to 0.2% to 1% of the general population.<sup>208</sup> The significant correlation between vitiligo and T1D might result from a similar pathogenesis of autoreactive cytotoxic T-cell mediated destruction in both diseases.<sup>209</sup> The destruction of melanocytes may be mediated by cytotoxic CD8 T-cells. Measurement of 25-hydroxyvitamin-D levels and supplementation should be considered, since vitamin D deficiency is common in people with vitiligo.<sup>210</sup> Treatment of vitiligo is often unsatisfactory. Individuals with diabetes 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 Ultraviolet-B-light-treatment may be effective for generalized vitiligo.<sup>211</sup>

### 5.2.3 | Other diabetes-related skin conditions

Other diabetes-associated skin conditions include granuloma annulare, diabetic dermopathy, acquired perforating dermatosis, and bullousis diabetorum, or diabetic bullae. There are also other skin disorders that occur more frequently in individuals with diabetes, such as pruritus, xerosis, lichen planus, finger pebbles, and skin tags.<sup>146,212</sup> Hyperglycemia leads to important metabolic and immunological alterations, so that people with diabetes tend to be more susceptible to skin infections.<sup>212</sup>

### 5.2.4 | Limited joint mobility in childhood diabetes

The cause of limited joint mobility (LJM) is the deposition of abnormal collagen in the connective tissues around the joints. The condition is also known as diabetic cheiroarthropathy and is linked to long-standing diabetes mellitus and suboptimal diabetes management. The prevalence is 8% to 58% in individuals with diabetes<sup>213</sup> and increases with age.<sup>214,215</sup> The risk of developing LJM is related to higher HbA1c levels.<sup>214</sup> LJM changes 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 are involved. The limitation is painless and non-disabling in most instances. Individuals with diabetes may present with an inability to firmly press the palmar surfaces of each of their hands together ("prayer sign") or against the surface of a table when their forearms are perpendicular to the surface of the table ("tabletop sign").<sup>216</sup> These changes occur as a result of periarticular expansion of connective tissue. In a recent study, ankle joint mobility (AJM) was evaluated using an inclinometer and found to be significantly reduced in youth with T1D, and both plantar and dorsiflexion was significantly lower in subjects with diabetes than in controls.<sup>217</sup> LJM is strongly associated with microvascular<sup>218</sup> and macrovascular changes and diagnosis of LJM should prompt a workup for related sequelae.<sup>219</sup> There is no curative treatment. Symptomatic people with diabetes may benefit from non-steroidal anti-inflammatory drugs or targeted injection of corticosteroids.<sup>220</sup> LJM is best managed with improved glycemic management as well as regular stretching to maintain and minimize further limitations in joint mobility.<sup>221</sup> Medical treatments targeting the formation of glycosylated end products accumulating on collagen and other connective tissues that are said to be responsible for the development of LJM, have so far proved to be unsuccessful.<sup>213</sup>

## 6 | BONE HEALTH AND TYPE 1 DIABETES

Accumulating evidence suggests that bone mineral density (BMD), bone structure, fracture risk and bone turnover markers (BTM), and bone metabolism are altered in T1D. Published results are, however, conflicting due to heterogeneity of the study populations in relation to age groups, metabolic outcomes, and method of BMD assessment. It has repeatedly been demonstrated that T1D is associated with an increased risk of fracture.<sup>222,223</sup>

A population-based cohort reported that risk of incident fracture in individuals with diabetes was higher across the lifespan 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 the rate was double in T1D adults as compared to healthy controls.<sup>222</sup> The risk for the increased fracture rate seems to be associated to lower BMD; however, other factors could also be at play.<sup>224–228</sup>

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 T1D, with potential biases including pubertal status, diabetes duration, and differing methods to assess BMD.<sup>224,229–232</sup> However, decreased trabecular BMD has been demonstrated by peripheral Quantitative CT (pQCT) measurements, assessing volumetric bone changes<sup>233,234</sup> and in pubertal T1D girls with normal BMD altered skeletal microstructure has been reported.<sup>235</sup> Data suggest microvascular disease mediates microarchitectural changes by increasing cortical porosity and is associated with lower bone turnover. There is no direct evidence linking microangiopathy to fracture incidence.<sup>236</sup> Finally, a bone health index<sup>237</sup> and bone geometry has been demonstrated to be altered in T1D children and associated to bone turn over markers.<sup>238</sup>

Furthermore, abnormal bone accrual (density and quality) in T1D<sup>239</sup> likely has a multifactorial etiology, involving reduced bone formation and abnormal bone quality.

The effect of increased HbA1c levels has consistently been demonstrated to be associated with low BMD<sup>229,230,232,240</sup> verified by a meta-analysis in 2021<sup>241</sup>; however, this observation was not confirmed in another recent meta-analysis.<sup>242</sup> As has been described in detail above, comorbidities such as CD and thyroid dysfunction can also negatively affect bone health in T1D,<sup>228</sup> but the true extent of their impact in children and adolescents is unclear.<sup>243</sup>

The influence of glucose metabolism on the regulation of bone metabolism seems to be complex and not yet fully known. Bone turnover markers (BTM) seem to be affected in T1D youth.<sup>244</sup> Altered BTM have been shown as early as within the honeymoon period of T1D in children and adolescents<sup>245</sup> with associations described between bone resorption and increased insulin sensitivity.<sup>246</sup> With longer T1D duration BTM also seems to be affected,<sup>247</sup> demonstrating increased bone resorption by increased levels of RANKL and lower OPG levels in 71 T1D individuals aged 5–18 years compared to 50 controls; however, OPG / RANKL data are conflicting in the literature. Another pediatric study demonstrated higher levels of CTX z-scores (another bone resorption marker) in 173 T1D children and adolescents aged 7–18 years of age to be associated to lower levels of HbA1c, also suggesting an interaction between bone and glucose metabolism.<sup>248</sup>

Regular assessment of bone health using bone densitometry is still controversial and not recommended. In specific populations, such as CD, evaluation of bone health should be considered, as the mechanisms involved in abnormal BMD in CD in association with T1D may not only be due to impaired absorption of calcium or vitamin D, but also include inflammatory pathways. In all youth with T1D, adequate nutrition including calcium, maintenance of normal vitamin D levels,

**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 T1D Presence of GAD autoantibodies CD	Antithyroid peroxidase antibodies, anti-thyroglobulin antibodies, TSH, T4 or free T4	At diagnosis (after glucose management is established): anti-thyroid peroxidase and anti-thyroglobulin 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 Suboptimal glycemic management	Age Duration of T1D Presence of GAD autoantibodies	Thyroid stimulating immunoglobulin, TSH, T4 or free T4, T3	Symptom related
Celiac disease	Most often asymptomatic Hypoglycemia Impaired linear growth Diarrhea Nausea, vomiting, abdominal pain	Affected first degree relative Other autoimmune disease	Tissue transglutaminase antibody Anti-endomysial antibody	Initial year of diagnosis 2–5 years intervals (sooner if symptomatic or First degree relative with CD)
Autoimmune gastric disease	Most often asymptomatic Anemia (pernicious anemia or iron deficiency anemia)	Thyroid autoimmunity Persistence of GAD autoantibody titers	Parietal cell autoantibodies (PCA) Blood count, vitamin B12, ferritin, gastrin	Symptom related
Primary adrenal insufficiency (Addison's disease)	Hypoglycemia Fatigue Nausea Weight loss Salt craving Postural hypotension Hyperpigmented skin and mucosa	First degree relative with disease	21-hydroxylase antibodies, Plasma ACTH, 8 AM serum cortisol, electrolytes, plasma renin activity	Symptom related
Vitiligo	Sharply delineated skin depigmentation, affecting extremities, face, and neck and trunk	Thyroid disorder autoimmune polyglandular syndrome (APS) and 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 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 diabetorum	Thickening of the skin with characteristic "peau d'orange" appearance		Clinical diagnosis	Symptom related

Abbreviations: ACTH, adrenocorticotrophic hormone; CD, celiac disease; GAD, glutamic acid decarboxylase antibodies; T1D, type 1 diabetes mellitus; T4, thyroxine; TSH, thyroid stimulating hormone.

and avoidance of smoking and regular weight-bearing exercise is important for bone health; however, more intervention studies are needed.<sup>249</sup> Screening for vitamin D deficiency, particularly in high-risk groups (CD, autoimmune thyroid disease, darker skin tone), should be considered in young people with T1D.

## 7 | ORAL HEALTH

Young people with T1D 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.<sup>250–253</sup> High blood glucose levels contribute to reduced salivary flow, which contributes to tooth decay and periodontal bone loss. Furthermore, there is evidence that elevated levels of pro-inflammatory mediators in sub-optimally managed diabetes and oxidative stress within the gingival tissues of people with diabetes play a role in the observed increased periodontal destruction.<sup>254</sup> Treatments for hypoglycemia such as sweetened carbonated beverages and candies may also increase the risk of tooth decay. In adults with T1D, suboptimal glycemic management is associated with an increased risk of future tooth loss.<sup>255</sup> Despite the increased risk, there is some evidence that children with diabetes have substandard oral hygiene practices.<sup>251</sup> Therefore, as part of preventive care, maintenance of oral health and regular dental review are recommended in young people with T1D.

### AUTHOR CONTRIBUTIONS

All authors engaged in multiple meetings and discussions and reviewed the relevant content and contributed to the writing and editing of this guideline.

### CONFLICT OF INTEREST

The authors have declared no relevant conflicts of interest.

### DATA AVAILABILITY STATEMENT

The relevant studies that support the recommendations are available in the references.

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