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Other complications and associated conditions in children and adolescents with type 1 diabetes

Elke Fröhlich-Reiterer, Nancy S Elbarbary, Kimber Simmons, Bruce Buckingham, Khadija N Humayun, Jesper Johannsen, Reinhard W Holl, Shana Betz and Farid H Mahmud

a Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria
b Department of Pediatrics, Ain Shams University, Cairo, Egypt
c Barbara Davis Center for Diabetes, University of Colorado, Denver, CO, USA
d Division of Endocrinology and Diabetes, Department of Pediatrics, Stanford University Medical Center, Stanford, CA.
e Department of Paediatrics and Child Health, Aga Khan University, Karachi, Pakistan.
f Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital, Herlev and Steno Diabetes Center Copenhagen, Copenhagen, Denmark
g Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
h Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany
i Parent/Patient advocate
j Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

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Corresponding author:
Prof Farid H Mahmud
Hospital for Sick Children
University of Toronto
Toronto
Canada
e-mail: farid.mahmud@sickkids.ca
1 What’s New/Changed

- Revised recommendations for celiac disease screening and biopsy that includes 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).

2 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).
- Screening for thyroid disease by measurement of TSH and anti-thyroid peroxidase antibodies is recommended at the diagnosis of diabetes once a patient 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 if a goiter develops, growth velocity is poor or other clinical signs or symptoms of thyroid disease are present (E).
- Celiac Disease (CD) may present with varied clinical signs and symptoms that may be gastrointestinal (including diarrhea, nausea, abdominal pain), extraintestinal (including
unexplained weight loss, iron-deficiency anemia, decreased bone mineralization, aphthous stomatitis) and/or diabetes-related (unexplained hypoglycemia) (B). It is recognized that the process of active case finding on the basis of symptoms can be challenging as CD is frequently asymptomatic in patients with type 1 diabetes.

- Screening for CD is recommended during the initial year of diabetes diagnosis and at 2-5 years intervals (C). 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. Persistent clinical signs and symptoms for CD or the availability of blood testing 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 (E).

- Measurement of human leukocyte antigen (HLA)-DQ2 and DQ8 is rarely helpful to exclude CD in patients with type 1 diabetes and not recommended as a screening test (B).

- Screening for IgA deficiency should be performed at the time of CD screening. In patients with confirmed IgA deficiency with 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 patients who are IgA deficient and 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 ≥ 10 times the upper limit of the TTG-IgA assay with confirmation of positive endomysial antibodies (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 ≥ 10 times the upper limit value within their measurement range, should be used. It is recognized that 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 a patient 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, patients should receive educational support from an experienced pediatric dietitian with knowledge of the Gluten-free diet (GFD) and both patients 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 type 1 diabetes including Addison’s disease, autoimmune
gastritis, juvenile idiopathic rheumatoid arthritis (JIA), other gastrointestinal diseases (e.g. Crohn’s disease, ulcerative colitis, autoimmune hepatitis), although the occurrence is rare (E).

Patients with T1D and adrenal diseases might have a greater risk of mortality, therefore these patients 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 are not recommended (E).

Patient education regarding proper injection techniques, rotation of injection sites with each injection and non-reuse of needles remains the best strategies to prevent lipohypertrophy and 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).
  - Routine clinical examination for skin irritation should be undertaken 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 (celiac disease, darker skin pigmentation) should be considered in young people with type 1 diabetes and treated using appropriate guidelines (E).

- Impaired bone health is an emerging long-term complication of type 1 diabetes for which optimization of calcium and vitamin D intake, avoidance of smoking and regular weight-bearing exercise should be counselled. Individualized assessments of bone health may be considered in children with medical co-morbidities such as celiac disease or 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. Greater height prior to and at diagnosis of T1D has been reported. \(^1\)\(^-\)\(^5\) The precise mechanism for this and whether or not this increased height is maintained is unclear, however, the observation that younger children have the highest BMI suggests that prenatal or early life triggers influence both height and weight gain before diabetes onset.\(^6\) In children who are auto-antibody positive, a sustained increased BMI is associated with an increased risk of progression to type 1 diabetes \(^7\) and high BMI has been identified as a risk factor for islet autoimmunity and subsequent development of type 1 diabetes,\(^8\)\(^,\)\(^9\) however not all reports confirm this. \(^10\)

There is considerable evidence that patients with very poor glycemic control show a decrease in height velocity, whilst better controlled patients maintain their height advantage. \(^11\) 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 insulin like growth factor binding proteins, and to promote growth. \(^12\)\(^,\)\(^13\) 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 and height outcomes, independent of glycemic control. The negative 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. Modern diabetes management seems to allow normal growth in the majority of patients. 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. Insulin insufficiency, celiac disease and other gastrointestinal disorders should also be considered in these cases. 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 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.

Once the child or adolescent has regained weight after the initial diagnosis of type 1 diabetes, 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. Historically, 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, potentially related to the impact of recurrent hypoglycemia. 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. Given that recent data from
multiple international registries show higher rates of overweightness and obesity in children and adolescents with type 1 diabetes compared with their non-diabetic peers, careful monitoring and management of weight gain based on BMI-charts for age and gender should be emphasized in diabetes care as obesity is a modifiable cardiovascular risk factor. \(^{25-27}\) A complex interplay between age, puberty, insulin requirement, metabolic control and BMI has to be taken into consideration. \(^{28}\) Use of adjunctive 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. \(^{29}\)

Girls seem to be more at risk of being overweight\(^ {21}\), a recognized risk factor for later development of eating disorders. \(^{30-32}\) In association with increased weight, there is also the risk of ovarian hyperandrogenism, hirsutism and polycystic ovarian syndrome. \(^{33,34}\) 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 be not long enough to impact hirsutism. \(^{35,36}\) 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.

Menarche may be delayed and menstrual irregularities together with hyperandrogenism increased 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. \(^ {37-39}\) Delayed menarche has also been associated with an increased risk of diabetic nephropathy and retinopathy (conflicting results), whereas early menarche was not. \(^ {40,41}\) A recent study indicated delayed menarche and
earlier menopause, resulting in a shorter reproductive period in females with type 1 diabetes, which might affect reproductive health and requires additional research. 42

4 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 (e.g. thyroid, celiac disease) in addition to islet autoantibodies, and approximately 25% of patients with type 1 diabetes are diagnosed with another autoimmune disease. 43 44-46 Comorbid autoimmune diseases occur more commonly in females compared to males and increase in incidence with age. 43 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. 43 Other autoimmune conditions more commonly diagnosed in patients with type 1 diabetes include primary adrenal insufficiency, collagen vascular disease (e.g. rheumatoid arthritis, lupus, psoriasis, scleroderma), other
gastrointestinal diseases (e.g. Crohn’s disease, ulcerative colitis, autoimmune hepatitis, autoimmune gastritis), and skin disease (e.g. 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. 47,48

4.1 Hypothyroidism/Hashimoto Thyroiditis

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 3–8% of children with type 1 diabetes. 49,50 The prevalence of autoimmune thyroid disease increases with age to approximately 20%, with the majority of patients having hypothyroidism. 43 Anti-thyroid 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. 44,50,51 Anti-thyroid antibodies are observed more frequently in girls than in boys and are associated with age, diabetes duration and pubertal maturity. 52 In addition, the presence of islet autoantibodies to GAD (Glutamic Acid Decarboxylase) and ZnT8 (Zinc Transporter-8) are associated with thyroid autoimmunity. 45 53 Screening children for anti-thyroid 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. 54

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 (e.g. diabetic ketoacidosis) or has suboptimal blood glucose control. In thyroid autoantibody positive, asymptomatic individuals, compensated hypothyroidism may also be detected, with a normal free T4 level and a mildly increased TSH. Treatment of thyroid disease in type 1 diabetes is the same as that used in the general population and is based on replacement with oral -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 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, LDL cholesterol and triglyceride levels. 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 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. 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. 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 anti-thyroid drug carbimazole or methimazole; which is the recommended treatment in children due to the increased risk of liver failure in patients treated with propylthiouracil. 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.

4.3 Celiac Disease

The prevalence of celiac disease ranges from 1–16.4% among children and adolescents with type 1 diabetes. An international comparison with 53,000 children and adolescents with type 1 diabetes across three continents reports a prevalence of biopsy proven celiac disease of 3.5%, with rates ranging from 1.9% in the U.S. to 7.7% in Australia. A recent report of the SWEET registry reports a mean prevalence of 4.5% with rates ranging from 1.9% in Asia/Middle East to 6.9% in Australia/New Zealand, 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 from the Middle East and Indian Subcontinent.

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. This association is common to both genders. The prevalence of CD increases with longer duration of diabetes.

Most cases of CD are diagnosed within the first year after T1D diagnosis and pediatric T1D
patients may develop CD within the first 5-10 years after T1D diagnosis. However, it is important to appreciate that the diagnosis of CDs can also be made beyond this period into adulthood. 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 new onset diabetes plus celiac disease may be challenging for children and their families.

CD is often asymptomatic and not necessarily associated with gastrointestinal symptoms, poor growth and/or deterioration in glycemic control or hypoglycemia. 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), extraintestinal symptoms (including iron-deficiency anemia, unexplained poor growth, weight loss, recurrent aphthous ulceration, decreased bone mineralization) and/or diabetes related symptoms (unexplained hypoglycemia). It is noted that tissue transglutaminase IgA (TTG-A) antibodies titers are higher in patients with gastrointestinal manifestations than asymptomatic ones.

Screening for CD is based on the detection of IgA antibodies (tissue transglutaminase (TTG-IGA) and/or endomysial (EmA)); both tests demonstrate sensitivity and specificity >90%. A report about the accuracy of screening tests could show, that threshold extrapolated from the general population for the diagnostic evaluation of CD are not suitable for use in asymptomatic T1D patients and that higher thresholds than the manufacturer recommendations are needed to optimize tests in asymptomatic T1D patients especially in the pediatric population. Laboratories reporting celiac disease-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 no longer recommended, given the high proportion of type 1 diabetes patients 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.  

IgA deficiency (which is present in 1:500 in the general population) is more common in people with type 1 diabetes and those with CD. 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-IgA and/or EmA is negative. If the child is IgA deficient, IgG-specific antibody tests (TTG IgG, EmA IgG, or DGP IgG (antibodies against deamidated gliadin protein)) need to be used for screening. This is important because CD may be more common in those with IgA deficiency than in the general population. All patients who are IgA deficient and who are 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 have suggested use of TTG-IgA as an initial screening test, with levels exceeding ≥ 10 times the upper limit of the TTG-IgA assay, with confirmation of positive endomysial antibodies (EMA IgA) in a second blood sample while on a diet containing gluten, can be used to diagnose CD. Only antibody tests with calibrator curve-based calculation, and having the TTG-IgA ≥ 10 times ULN value within their measurement range, should be used. It is recognized that approach has not been universally adopted as standard of care internationally and is inconsistent with other guidelines.

There is a clear statement that in patients with positive TTG-IgA <10x ULN a small bowel biopsy with at least 4 biopsies from the distal duodenum and at least 1 from the bulb should be taken to confirm the diagnosis of celiac disease by demonstrating subtotal villus atrophy, as
outlined in the Marsh Classification. 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.

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 (GFD), and resolution of symptoms.

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 a patient 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.

There are challenges to broader implementation of assay cutoffs for diagnostic purposes that include a lack of international standardization, assay variability as well as celiac and diabetes related factors. This includes the fact that elevations in TTG-IgA positivity at the time of screening may be transient and there are several reports of spontaneous normalization of CD antibodies emphasizing serological follow-up (3-6 months) instead of immediate duodenal biopsy and the need of a duodenal biopsy to verify the diagnosis especially in asymptomatic patients.

Children with coexisting type 1 diabetes 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, indicating a need to regularly assess the serum lipid profile, annual screening of thyroid function and regular screening for depression and eating disorders in children and adolescents with both
conditions. 99-101

A GFD normalizes the bowel mucosa, frequently leads to disappearance of antibodies and has an impact on the normalization of lipid profile 102,103, but may not necessarily impact glycemic control. 71,77,104 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 patients and their diabetes care team should be vigilant as insulin requirements may change during transition to the GFD. 105 106 The aims of the GFD also include reduction of the possible risk of subsequent gastrointestinal malignancy and conditions associated with subclinical malabsorption that may include osteoporosis, iron deficiency, and growth failure. 71,107,108 Long-standing celiac disease in the context of type 1 diabetes may be associated with an increased risk of retinopathy 109, while non-adherence to a GFD may increase the risk of albuminuria. 110,111 There are also reports of increased risk for microvascular and potentially for macrovascular complications in T1D patients with comorbid CD. 112-114

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 patients and families should be made available, that address both dietary issues and adaptation to a GFD in home, school and social settings. 115 Online education for GFD teaching has been shown to be a helpful tool in teaching families with T1D and CD.116

Children and adolescents with T1D, with poor adherence to a GFD may have a reduced
quality of life, worse glycemic control and lower height SDS, \cite{103,117} although diabetes related factors such as HbA1c and symptoms are important drivers of lowered QOL in type 1 diabetes patients with both conditions.\cite{118}

The prevalence of CD 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 CD should also be screened.\cite{98}

4.4 Primary adrenal insufficiency (Addison’s disease)

Up to 2\% of patients with type 1 diabetes have detectable anti-adrenal autoantibodies.\cite{44,119,120} The HLA DRB1*04-DQB1*0302 (primarily DRB1*0404) and DRB1*0301-DQB1*0201 haplotypes define high-risk subjects for adrenal autoimmunity,\cite{121} 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.\cite{122} A person with type 1 diabetes who has the DRB*0404 allele and 21-hydroxylase antibodies has a 100-fold risk of developing Addison’s disease may be associated with type 1 diabetes as part of the Autoimmune Polyglandular Syndromes (APS-1 and APS-2).\cite{123} 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.\cite{124,125}

Addison’s disease is suspected by the clinical picture of frequent hypoglycemia (with a
potential concomitant increase in glucagon use), unexplained decrease in insulin requirements, increased skin pigmentation, lassitude, weight loss, hyponatremia and hyperkalemia as well as severe or recurrent infections. The diagnosis is based on the demonstration of a low cortisol response to an ACTH stimulation test and positive anti-adrenal (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, a rising ACTH level suggests a failing adrenal cortex and the development of primary adrenal insufficiency. Longer term data has shown a four-fold greater risk of mortality in patients with both diabetes and adrenal disease, as compared with diabetes alone. These data emphasize this is a special patient population that requires additional vigilance to balance the challenges of diabetes care, optimizing metabolic outcomes, reducing risks of hypoglycemia and diabetic ketoacidosis, with appropriate management and prevention of adrenal crises. It is important to prevent adrenal crises by patient education, emergency cards, and adjustment of the glucocorticoid treatment in case of surgery or medical procedures, as well as to identify and treat adrenal crises in a timely manner.

4.5 Autoimmune Gastritis

Parietal cell antibodies (PCA) are the principal immunological markers of autoimmune gastritis and react against the H⁺/K⁺ ATPase of the gastric parietal cells. 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. Parietal cell antibodies may also inhibit intrinsic factor secretion, leading to vitamin B12 deficiency and pernicious anemia. Type 1 diabetes is associated with an increased risk of parietal cell antibody positivity, with
prevalence rates of parietal cell antibodies in children ranging from 5.3%-7.5%.\textsuperscript{132-134} 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. In patients with positive PCA, blood count, iron status and Vitamin B12 status should be measured. If the patient with positive PCA has gastrointestinal symptoms a gastroscopy should be considered.

4.6 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, psoriasis and sarcoidosis may also develop in patients with type 1 diabetes.\textsuperscript{135} In children with T1D, JIA is the most frequently encountered non-organ-specific autoimmune condition.\textsuperscript{135} The disease was shown to affect girls twice as often as boys. Literature provides 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.\textsuperscript{136} Sjögren’s syndrome is a systemic autoimmune disease mostly affecting lacrimal and salivary glands. The spectrum of the disease ranges from dryness syndrome to systemic disease of exocrine glands. Literature provides single reports of the development of diabetes in Sjögren’s syndrome.\textsuperscript{137}

4.7 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.\textsuperscript{138,139} Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare autosomal recessive disease caused by mutations of the Autoimmune Regulator (AIRE) gene. The clinical diagnosis is defined by the presence of at least two components of the classic triad including chronic mucocutaneous candidiasis, chronic hypo-parathyroidism, and AD. Other common features of the disease are hypergonadotrophic hypogonadism, alopecia, vitiligo, autoimmune hepatitis, type 1 diabetes, and gastrointestinal dysfunction.\textsuperscript{140}

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 patient: autoimmune 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. APS-2 is usually associated with class II HLA alleles, particularly DRB1*0401 and DRB1*0404.\textsuperscript{124} The prevalence of type 1 diabetes is 4% to 20% in APS-1 and 60% in APS-2.\textsuperscript{141,142} Approximately 3 to 8% of patients with type 1 diabetes mellitus or autoimmune thyroid disease have CD.\textsuperscript{143} The female-to-male predominance of patients with type 1 diabetes mellitus and thyroid disease is much greater (6.4 to 1) than the ratio for patients with diabetes alone (1 to 1).
5 Type 1 Diabetes Related Skin Conditions

5.1 Skin problems related to diabetes therapy and chronic devices use

5.1.1 Insulin-induced lipodystrophy (Lipo hypertrophy and lipoatrophy)

Insulin-induced lipodystrophy remains an important complication in the care of diabetes. Lipohypertrophy and lipoatrophy represent well-recognized dermatological complications of subcutaneous insulin administration. The need for improved awareness of physicians to recognize these insulin-related skin complications should be highlighted.

Lipohypertrophy

Lipohypertrophy (LH) is a frequent complication of insulin therapy characterized by fibrous and poorly vascularized lesions in the subcutaneous adipose tissue confined to frequently used insulin injection sites in form of painless induration and swelling. A recent study denoted higher levels of proinflammatory cytokines and anti-insulin antibody are associated with lipodystrophy in type 1 diabetes.

With regards to etiology, two main local factors are involved: tissue trauma caused by poor injection habits and technique, including insufficient injection site rotation, injections into lipodystrophic lesions, small injection 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 LH pathogenesis. As lipo hypertrophic areas are relatively painless, patients 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 areas used for injection is recommended to
appreciate the soft, lipoma-like nodules. 149

There are important metabolic consequences of LH that include poor glucose control and glycemic variability that may increase the risk of diabetes complications.150 In addition, the presence of LH is associated with the need for increased insulin doses due to reduced insulin absorption by up to 25% and variable glycemic excursions related to alterations in insulin action duration. 151 Patients with LH were found to have a 7-times higher risk of unpredictable unexplained hypoglycemia than patients without LH. 145

In LH prevention, the proper insulin delivery techniques, including regular injection site rotation, avoidance of already affected areas, and limited insulin needle reuse, is essential. 152 Practical considerations, such as needle lengths being as short as possible to minimize tissue trauma and avoid inadvertent intramuscular administration, especially in thin individuals, should be considered.153 Smaller 4 mm needles have been reported to carry the least risk of tissue trauma and avoid intramuscular injection, but choice of needle size must be individualized. 154

Ultrasound has also been used for evaluation of insulin-induced LH.155 The method is more sensitive compared to palpation whereby ultrasound-verified LH was detected in more than 80% of cases. In patients with significant, wide-spread LH ultrasound can be used to find suitable sites for injections (“ultrasound injection map”). In everyday practice, physical examination of injection sites and evaluation 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. 156
Lipoatrophy

Lipoatrophy (LA) is a form of localized lipodystrophy in form of localized loss of subcutaneous adipose tissue at the site of insulin injection and a recognized complication of insulin therapy. 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.157,158

The mechanism of LA is generally poorly understood although an immune pathogenesis seems likely, and it is seen more often in patients who have other signs of autoimmunity.159 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.160 Repeated use of the same insulin injection site and multiple usage of the same pen needle increases the risk of lipoatrophy.161

Treatment options are limited and may include changing the site of injection or CSII and switching insulin analogues 162 however, these are not always effective in complete resolution of lesions.163,164 Treatment with steroids, given orally (daily low-dose prednisolone) 163 or injection of dexamethasone 164 and cromolyn sodium 158 into the lipoatrophic lesions had been reported successfully in anecdotal cases.165 166

5.1.2 Dermatological manifestations of diabetes technology devices: Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM)

Continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) devices are widely used in patients with type 1 diabetes as standard therapy or as part of a closed-
loop-systems as they may improve glycemic control and enhance treatment flexibility \textsuperscript{167}. With increasing popularity, a wide range of reported skin reactions and dermatological complications to CSII and CGM devices are frequently reported in clinical practice and additional CGM and CSII specific skin concerns are described in Chapters 16 (CGM) and 17 (CSII) of ISPAD 2022 guidelines.

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\% \textsuperscript{168-170}, which may affect adherence and may remain a barrier to consistent long-term use. A recent systematic review of cutaneous complications in CGM users from clinical trial data reported erythema (55\%), followed by itching/pruritus (11\%) and induration (9\%).\textsuperscript{171} With regards to CSII, localized eczematous reactions at the site of pump insertion were noted in 14\% of youth in one study \textsuperscript{172} while a survey of 143 youth documented that nearly half of the cohort reported non-specific eczema.\textsuperscript{173}

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.\textsuperscript{174,175} In addition, varying degrees of contact dermatitis can occur on the manufacturer adhesives to colophonium and N, N-dimethylacrylamide.\textsuperscript{175-177} Acquired leukoderma, with localized areas of depigmentation, have been described with direct skin contact and has been linked to the depigmenting substance hydroquinone monomethyl ether (HMME).\textsuperscript{178} There is a need for manufacturing changes to improve breathability and reduce trapped moisture that contribute to skin reactions with the current technologies.\textsuperscript{179} Initiatives for full and accurate labelling of the chemical composition of devices were recently presented.\textsuperscript{180}
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.\textsuperscript{160,181}

CSII can lead to lipodystrophy, whereas lipoatrophy is less common than lipohypertrophy.\textsuperscript{161,164} CGM use is not thought to contribute to lipodystrophy and a previous study indicated that CGM accuracy is not compromised in LH.\textsuperscript{182}

The prevention of these skin related complications includes good nutrition, hydration, site rotation, correct device placement, accurate removal technique and prophylactic skin care for optimal skin integrity.\textsuperscript{183} Skin preparation suggestions 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 prior to insertion for those with known prior reactions (e.g. fluticasone).\textsuperscript{184} Sweating could be mitigated by applying antiperspirant to the skin before insertion.\textsuperscript{185} Removal of adhesives by including use of removal agents and techniques could be also used to minimize tissue damage. Moreover, patients should be taught to monitor sites for pain, edema, erythema, warmth, or suppuration.

5.1.3 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\textsuperscript{186} or following a high-dose insulin therapy
among diabetes patients with poor nutrition. The true incidence of insulin edema is not known and insulin edema is reported most often among children and adolescents. Despite its self-limiting nature, it is rarely observed with pleural effusion, heart failure, or generalized edema. The mechanisms resulting in insulin edema is the deficiency of insulin, which results in a catabolic state. Chronic hyperglycemia has been shown to result in . Intensive fluid resuscitation during the initial phase of treatment may lead to extravasation of the fluid into the subcutaneous tissue, exacerbating edema.

Moreover, the severity of edema negatively correlates with BMI, with the most severe cases occurring in the severely underweight patient, further suggesting the link between the resolution of the catabolic state upon the commencement of insulin and the development of edema.

The management of insulin edema requires the early identification of patients at high risk for the development of severe complications. Insulin edema often improves spontaneously in 1 to 3 weeks and decreased insulin doses can also help to reduce edema. Short-term diuretic treatment, salt restriction, and ephedrine have been described and may be effective in the treatment of acute edema, but are rarely indicated. The reintroduction of insulin necessary for the management of type 1 diabetes should be gradual and accompanied by a frequent reassessment of fluid status.

5.2 Dermatological conditions associated with diabetes

5.2.1 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.\textsuperscript{197,198} The prevalence of NL ranges from 0.3\% to 1.2\% among patients with diabetes mellitus \textsuperscript{199}, of which two-thirds have type 1 diabetes. NL is generally asymptomatic unless it is ulcerated and painful in 25\% to 33\% of cases.\textsuperscript{200} NL is more common in females than in males.\textsuperscript{201}

NL usually appears during young and middle adulthood\textsuperscript{202}, although there are a few studies reporting cases in childhood and adolescents.\textsuperscript{203,204} The pretibial region is the area typically affected and only rarely on hands, fingers, face, forearms and scalp\textsuperscript{201} and recently reported also in trunk.\textsuperscript{205} It has been suggested that 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 NL lesion remains controversial with limited data available in the pediatric population.\textsuperscript{206}

The treatment of NL 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.\textsuperscript{207} Some authors have reported a beneficial effect from smoking cessation and improved blood glucose control.\textsuperscript{208}

In case reports, doxycycline,\textsuperscript{209} anti-TNFα agents,\textsuperscript{210} JAK1/2 inhibitor\textsuperscript{211} showed promising results in the management of this condition.

### 5.2.2 Vitiligo

Vitiligo vulgaris, or skin depigmentation, occurs more commonly in type 1 diabetes. 1\% to 7\% of all diabetic patients have vitiligo compared to 0.2\% to 1\% of the general population.\textsuperscript{212} The significant correlation between vitiligo and type 1 diabetes might result from a similar
pathogenesis of autoreactive cytotoxic T-cell mediated destruction in both diseases.\textsuperscript{213} 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.\textsuperscript{214} 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.\textsuperscript{215}

5.2.3 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.\textsuperscript{149,216} Hyperglycemia leads to important metabolic and immunological alterations, so that people with diabetes tend to be more susceptible to skin infections.\textsuperscript{216}

5.2.4 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 is also known as diabetic cheiroarthropathy and linked to long-standing diabetes mellitus and poor diabetes control. The prevalence is 8% to 58% in patients with diabetes \textsuperscript{217} and increases with age.\textsuperscript{218,219} The risk of developing limited joint mobility was related to higher HbA1c levels.\textsuperscript{218}

Limited joint mobility 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 were involved. The limitation is painless and non-disabling in most instances. Patients 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”). These changes occur as a result of periarticular enlargement of connective tissue. Ankle joint mobility (AJM) was evaluated using an inclinometer in a recent study where AJM was significantly reduced in young type 1 diabetes patients and both plantar and dorsiflexion was significantly lower in subjects with diabetes than in controls.

LJM is strongly associated with microvascular and macrovascular changes and diagnosis of LJM should prompt a workup for related sequela. There are no curative treatments. Symptomatic patients may benefit from non-steroidal anti-inflammatory drugs or targeted injection of corticosteroids. LJM is best managed with improved glycemic control, as well as, regular stretching to maintain and minimize further limitations in joint mobility. 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.

6 Bone Health and Type 1 Diabetes

Accumulating evidence suggest 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 population in relation to age groups,
metabolic outcomes and method of BMD assessment. It is repeatedly demonstrated that type 1 diabetes is associated with an increased risk of fracture.\textsuperscript{226,227}

A population-based cohort 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 the rate was double in type 1 diabetes adults as compared to healthy controls.\textsuperscript{226} The risk for the increased fracture rate seems to be associated to lower BMD, however other factors could also be at play.\textsuperscript{228-232}

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 BMD.\textsuperscript{228,233-236} However, decreased trabecular BMD has been demonstrated by peripheral Quantitative CT (pQCT) measurements, assessing volumetric bone changes\textsuperscript{237,238} and in pubertal T1D girls with normal BMD altered skeletal microstructure has been reported.\textsuperscript{239} 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.\textsuperscript{240} Finally, a bone health index\textsuperscript{241} and bone geometry has been demonstrated to be altered in T1D children and associated to bone turn over markers.\textsuperscript{242}

Furthermore, abnormal bone accrual (density and quality) in type 1 diabetes\textsuperscript{243} likely has a multifactorial etiology, involving reduced bone formation and abnormal bone quality. The effect of increased HbA1c levels has consistently been demonstrated to associate to low BMD\textsuperscript{233,234,236,244} verified by a meta-analysis from 2021,\textsuperscript{245} however, was not confirmed in another recent meta-analysis.\textsuperscript{246} 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.

The influence of glucose metabolism on the regulation of bone metabolism seems to be complex and not yet fully known. The bone turn-over markers (BTM) seem to be affected in T1D youth. As early as within the honey moon period of T1D in children and adolescents altered BTM have been observed and associated to the preserved beta-cell function and outcome of the remission phase the later study suggesting an association between bone resorption and increased insulin sensitivity. With longer T1D duration BTM also seems to be affected, demonstrating increased bone resorption by increased levels of RANKL and lower OPG levels in 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 of to be associated to lower levels of HbA1c, also suggesting an interaction between bone and glucose metabolism.

Regular assessment of bone health using bone densitometry is still controversial and not recommended. In specific populations, such as celiac disease, evaluation of bone health should be considered, as the mechanisms involved in abnormal BMD in celiac disease in association with T1D may not only be due to potential impaired absorption of calcium and or vitamin D, but also include inflammatory pathways. 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 is important for bone health, however more intervention studies are needed. 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.

7 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.\textsuperscript{254-257} 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.\textsuperscript{258} Despite the increased risk, there is some evidence that children with diabetes have poor oral hygiene practices.\textsuperscript{255} Therefore, as part of preventive care, maintenance of oral health and regular dental review are recommended in young people with type 1 diabetes.

TABLE 1. Summary of Common Complications and Associated Conditions in Children and Adolescents with Type 1 Diabetes

<table>
<thead>
<tr>
<th>Comorbid Autoimmune Disease</th>
<th>Symptoms</th>
<th>Risk Factors</th>
<th>Screening and Confirmatory Tests</th>
<th>Screening Recommendations</th>
</tr>
</thead>
</table>
| Hashimoto’s Thyroiditis     | • Decreased linear growth  
• Painless goiter  
• Fatigue  
• Cold intolerance  
• Bradycardia | • Age  
• Duration of T1DM  
• Presence of GAD autoantibodies | • Antithyroid peroxidase antibodies, antithyroglobulin antibodies, TSH, T4 or free T4 | • At diagnosis (after glucose control established): antithyroid peroxidase and anti-thyroglobulin |
| 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  
• Initial year of diagnosis  
2-5 years intervals (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 autoantibody titers | • Parietal cell autoantibodies (PCA)  
Blood counts, vitamin B12, ferritin, gastrin  
• Symptom related |
| Primary Adrenal Insufficiency (Addison’s Disease) | • Hypoglycemia  
• Fatigue  
• Nausea  
• Weight loss  
• Salt craving  
• Postural hypotension | • First degree relative with disease | • 21-hydroxylase antibodies, ACTH, fasting am cortisol, electrolytes, plasma, renin  
• Symptom related |
<table>
<thead>
<tr>
<th><strong>Vitiligo</strong></th>
<th>• Hyperpigmentation of skin and mucosa</th>
<th>• Thyroid disorder autoimmune polyglandular syndrome (APS) and vitamin D deficiency</th>
<th>• Clinical Diagnosis</th>
<th>• Symptom Related</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alopecia</strong></td>
<td>• Sharply delineated skin depigmentation, affecting extremities, face, and neck and trunk.</td>
<td>• Polyglandular autoimmune syndrome type 2</td>
<td>• Clinical Diagnosis</td>
<td>• Symptom Related</td>
</tr>
<tr>
<td><strong>Juvenile Idiopathic Rheumatoid Arthritis</strong></td>
<td>• Non-scarring, round and/or oval patches of hair loss.</td>
<td>• Polyglandular autoimmune syndrome type 2</td>
<td>• Clinical Diagnosis</td>
<td>• Symptom Related</td>
</tr>
<tr>
<td><strong>Sjogren Syndrome</strong></td>
<td>• Joint(s) inflammation characterized by swelling, limitation in the range of motion, tenderness; symptoms must be present for at least 6 weeks</td>
<td>• Clinical Diagnosis</td>
<td>• Symptom Related</td>
<td></td>
</tr>
<tr>
<td><strong>Psoriasis</strong></td>
<td>• Xerophthalmia (dry eyes) and xerostomia (dry mouth); recurrent parotitis, with other organ involvement</td>
<td>• Clinical Diagnosis</td>
<td>• Symptom Related</td>
<td></td>
</tr>
<tr>
<td><strong>Sarcoidosis</strong></td>
<td>• Skin disorder with thick, red, bumpy patches covered with silvery scales</td>
<td>• Clinical Diagnosis</td>
<td>• Symptom Related</td>
<td></td>
</tr>
<tr>
<td><strong>Sclerodema diabeticorum</strong></td>
<td>• Non-caseating granulomas, predominantly in the lymph nodes, lungs, eyes and skin.</td>
<td>• Clinical Diagnosis</td>
<td>• Symptom Related</td>
<td></td>
</tr>
</tbody>
</table>

GAD: Glutamic Acid Decarboxylase Antibodies; T1DM: type 1 diabetes mellitus; TSH: thyroid stimulating hormone; T4: thyroxine; ACTH: adrenocorticotropic hormone
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