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Autoimmune disorders associated with type 1 diabetes: clinical overview and principles of management

Zaburzenia autoimmunologiczne związane z cukrzycą typu 1 – przegląd kliniczny i zasady postępowania

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Abstract

Type 1 diabetes mellitus is an autoimmune disease in which patients with a genetic predisposition develop antibodies against pancreatic islet β-cells under certain conditions, resulting in the loss of insulin production. Genetic, infective, dietary, and humoral factors are potential predictors associated with the risk of β-cell destruction. The coexistence of another autoimmune disease can be found in up to 29% of patients with type 1 diabetes. The most common disorders are autoimmune thyroid disease, coeliac disease, autoimmune gastritis, pernicious anaemia, and vitiligo. Other conditions that can coexist with type 1 diabetes are rheumatoid arthritis, autoimmune hepatitis, alopecia, and psoriasis. This coexistence is often present in autoimmune polyendocrine syndromes. The likelihood of developing an autoimmune disease increases with age, and it is higher in the female population. Concomitant autoimmune diseases can negatively affect the patient's quality of life and metabolic control of diabetes, potentially increasing the risk of micro- or macrovascular complications and the frequency of hypoglycaemic episodes. Determining organ-specific antibodies is useful in the active search for autoimmune diseases in type 1 diabetes patients to identify individuals at increased risk for the disease. This article aims to summarise the most recent research on type 1 diabetes-associated autoimmune disorders, including screening, diagnosis, and treatment principles.

Keywords: autoimmune thyroid diseases, type 1 diabetes mellitus, autoimmune disorders, coeliac disease

Streszczenie

Cukrzyca typu 1 jest chorobą autoimmunologiczną, w której predysponowani genetycznie pacjenci wytwarzają przeciwciała przeciwko komórkom β wysp trzustkowych, co prowadzi do bezwzględnego niedoboru insuliny. Zarówno czynniki genetyczne, infekcyjne, dietetyczne, jak i humoralne są potencjalnymi czynnikami predykcyjnymi związanymi z ryzykiem zniszczenia komórek β wysp trzustkowych. Współwystępowanie innej choroby autoimmunologicznej można stwierdzić nawet u 29% pacjentów z cukrzycą typu 1. Najczęstsze choroby to autoimmunologiczna choroba tarczycy, celiakia, autoimmunologiczne zapalenie błony śluzowej żołądka, niedokrwistość złośliwa i bielactwo nabyte. Inne choroby, które mogą współistnieć z cukrzycą typu 1, to reumatoidalne zapalenie stawów, autoimmunologiczne zapalenie wątroby, łysienie oraz łuszczyca, często współwystępujące w przebiegu autoimmunologicznych zespołów niedoczynności wielogruczołowej. Prawdopodobieństwo rozwoju choroby autoimmunologicznej wzrasta wraz z wiekiem i jest wyższe w populacji kobiet. Współistniejące choroby autoimmunologiczne mogą negatywnie wpływać na jakość życia pacjenta, a także na kontrolę metaboliczną cukrzycy, potencjalnie zwiększając ryzyko zarówno powikłań mikro- lub makroangiopatycznych, jak i częstotliwość epizodów hipoglikemii. Oznaczanie przeciwciał swoistych narządowo jest wykorzystywane w aktywnym poszukiwaniu chorób autoimmunologicznych u pacjentów z cukrzycą typu 1 w celu identyfikacji pacjentów ze zwiększonym ryzykiem wystąpienia choroby. Niniejszy artykuł ma na celu podsumowanie najnowszych badań dotyczących zaburzeń autoimmunologicznych związanych z cukrzycą typu 1 u predysponowanych pacjentów, w tym badań przesiewowych, rekomendowanej diagnostyki i zasad leczenia.

Słowa kluczowe: autoimmunologiczne choroby tarczycy, cukrzyca typu 1, zaburzenia autoimmunologiczne, celiakia

INTRODUCTION

Type 1 diabetes mellitus (T1DM), accounting for 5–10% of diabetes cases, is a disease caused by the destruction of pancreatic β-cells by an autoimmune process, usually leading to absolute insulin deficiency. The process is initiated when environmental factors trigger T-cell and humoral autoimmune responses against beta cells in people with a genetic predisposition. The disease manifests itself when 80–90% of pancreatic beta cells are damaged, which, through a significant insulin deficit, causes hyperglycaemia, resulting in a series of rapidly progressive symptoms[1]. Genetic, infective, dietary, and humoral factors are potential predictors associated with the risk of beta cell destruction. Due to the disease's multifactorial nature, these factors may not be seen as separate entities but rather as parts of a spectrum and interactive determinants which, when combined, could significantly increase the risk of developing the disease[2]. Autoimmune processes might not be limited to pancreatic islet cells. Therefore, antibody-mediated autoimmune diseases are prevalent among T1DM patients. The most common autoimmune disorder (AID) associated with T1DM is autoimmune thyroid disease (AITD), found in 17–30% of patients. Less frequent AID include coeliac disease (CD; 1.9–10% cases), autoimmune gastritis (AIG) and/or pernicious anaemia (PA; 0.3–5% cases), vitiligo (2.4%), and Addison's disease (AD; 0.2–0.4%). Other conditions that can coexist with T1DM are rheumatoid arthritis, autoimmune hepatitis, alopecia, and psoriasis. The coexistence is often present in autoimmune polyendocrine syndromes (APS). The likelihood of developing an AID increases with age, and it is higher in the female population[3]. According to the American Diabetes Association (ADA) guidelines, it is recommended to search for additional autoimmune conditions soon after the diagnosis of T1DM, and if symptoms develop[4].

AUTOIMMUNE THYROID DISEASES

AITD and T1DM are the most frequent AID, coexisting in 17–30% of patients[4–6]. Clinically, they can be manifested as either hypothyroidism or hyperthyroidism[7]. The pathogenesis of AITD involves humoral and cellular autoimmune mechanisms acting against the thyroid gland[6]. AITD is characterised by dysfunctional auto-antigen monitoring and autoreactive immune responses by T, B lymphocytes, macrophages, and dendritic cells, resulting in the production of specific autoantibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TGAb)[6,7]. In an analysis of nearly 14,000 patients with T1DM conducted by Gimenez-Perez et al., AITD was found in 18.3% of individuals[8], while in the study by Bao et al. involving nearly 59,000 patients – in 20.1%, making AITD the most common AID accompanying T1DM[9]. The most frequent presentations of AITD include Graves' disease (GD) and Hashimoto's thyroiditis (HT)[5], which may coexist or occur in a single patient at different stages of the disease[6]. Latent autoimmune diabetes in adults (LADA) is an independent factor in developing AITD[6]. At the time of T1DM diagnosis, about 25% of paediatric patients already have a positive titre of antithyroid antibodies[4]. Interestingly, the Kakleas et al. study revealed that the presence of one type of antithyroid antibody increased the likelihood of developing another type; a positive titre of antibodies to glutamic acid decarboxylase (anti-GAD) itself was associated with a twofold higher risk of developing thyroid autoimmunity[10]. A similar association with the presence of anti-GAD antibodies was noted in the Kordonouri et al. study; however, the risk of developing AITD was increased threefold compared to anti-GAD-negative patients[11]. In adult patients with T1DM, TPOAb are present in 15–30%[5]. Approximately 50% of patients with T1DM and a positive TPOAb titre develop AITD[5]. In a retrospective study evaluating 121 paediatric patients with T1DM, during the follow-up period, a total of 30 patients developed AITD, of which seven developed the disease clinically and required levothyroxine substitution[3]. Overall, however, hypothyroidism is more common, occurring in about 0.5% of patients with T1DM[4]. In adult patients, the peak incidence of GD is in the fourth, while HT is in the fifth and sixth decades of life[5]. In a review by Nederstigt et al., based on 180 articles, including an analysis of 293,889 patients with T1DM, hypothyroidism was found in 9.8% of patients, highlighting an increase in incidence for each additional ten years of patient age[12]. A close link was also demonstrated by Mäkimattila et al., indicating that late-onset T1DM, and ageing of the patient, increase the risk of hypothyroidism[13]. Similarly, the Kakleas et al. study revealed that the incidence of antithyroid antibodies was related to diabetes duration and age, with a one-year increase in patient age elevating the likelihood of antithyroid antibodies by as much as 15%[10]. In a review by Nederstigt et al., hyperthyroidism was found in 1.3% of patients with T1DM[12], and it was still more common in the group of patients with T1DM than in the general population[14]. Indeed, subclinical hyperthyroidism is diagnosed in only 0.12% of the non-diabetic population, but in 6–10% of patients with T1DM[5]. In addition to T1DM, AITD may exist in isolation or coexist with other AID, such as CD, alopecia areata, or vitiligo[15]. Co-occurrence of at least two autoimmune glandular disorders is defined as autoimmune polyendocrinopathy (AP)[5]. The most common type of AP, involving coexisting T1DM and AITD, is variant autonomic polyglandular syndrome type 3 (APS-3)[16] with a peak incidence in the fourth and fifth decades of life, predominantly in women[5]. Co-occurrence of T1DM and AITD can also be observed in the course of sporadic juvenile APS type 1 and adult APS type 2, with AD as the primary hormonal component[16]. Although the exact pathogenic mechanisms have not been fully detailed, the inheritance pattern appears to be autosomal dominant with incomplete penetrance, with the

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possibility of interaction of several genetic loci with environmental factors including vitamin D deficiency, excessive iodine supply, selenium deficiency, exposure to radiation and contrast agents, pregnancy or infectious agents such as *Yersinia enterocolitica*[5,17]. Several studies have also reported an association between childhood enteroviruses and *Helicobacter pylori* infection, which clearly highlights the role of environmental factors in the pathogenesis of AITD and T1DM[6]. In addition, genetic syndromes, such as Turner syndrome, trisomy of chromosome 21, Down syndrome, or Klinefelter syndrome, are associated with an increased susceptibility to AID, including T1DM and AITD[15]. Despite the available knowledge, many aspects in the pathogenesis of T1DM and AITD have not been fully clarified.

According to the ADAs 2023 recommendations, the evaluation of TPOAb and TGAb should be considered immediately after diagnosing T1DM[4]. Thyroid-stimulating hormone (TSH) levels should be assessed during clinical stabilisation or shortly after normalisation of glycaemia, due to the risk of impact on thyroid function of the euthyroid sick syndrome, hyperglycaemia, history of ketoacidosis, ketosis, or weight loss[4]. If TSH levels remain within the reference range, another evaluation should be performed every two years, or sooner if an antithyroid antibody titre is positive or clinical signs of thyroid dysfunction appear[4,14].

Nevertheless, according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) Guidelines, symptomatic hypothyroidism may not significantly affect diabetes control[14], and no statistically significant differences in HbA_{1c} have been shown for isolated T1DM versus T1DM coexisting with AID[18]. Both ISPAD and ADA state that already subclinical hypothyroidism increases the risk of symptomatic hypoglycaemia, while hyperthyroidism complicates satisfactory glycaemic control[4,14]. It is recommended that patients who, despite adequate treatment, persistently cannot achieve good control of their underlying disease should be screened for coexisting AID[19]. Untreated thyroid dysfunction negatively affects the metabolic control in patients with T1DM, significantly impacting the ability to treat both comorbidities effectively[16]. The daily insulin dose in patients with HT was higher than in patients with isolated T1DM[18], although a review by Popoviciu et al. indicated that patients with hypothyroidism required lower insulin doses due to reduced hepatic glucose production[20]. An increase in insulin requirements and the risk of severe hyperglycaemia also applies to patients with coexisting GD, in whom the hypermetabolic state elevates energy requirements, thus resulting in increased gluconeogenesis, glycogenolysis, and lipolysis, as well as a decrease in tissue sensitivity to insulin[17,21]. Hyperthyroidism shortens the half-life of insulin due to the accelerated degradation rate and release of inactive insulin precursors[22]. It has been speculated that the association between severe hyperglycaemia and hyperthyroidism may also be explained by increased glucose absorption in the intestines, in which thyroid hormones are involved[20,21]. Successful treatment of thyroid dysfunction reduces the patient's requirement for insulin[17]. Diabetes in patients with GD also requires greater caution when using corticosteroids in patients with ophthalmopathy due to their unfavourable metabolic profile[20]. It is clinically significant that thyrotoxicosis often precedes the onset of ketoacidosis[21].

In patients with coexisting HT, diabetic retinopathy occurred less frequently than in isolated T1DM, while in GD it was more common[18]. In GD and HT, microalbuminuria appeared less regularly, while neuropathy occurred more often than in isolated T1DM[18]. Moreover, neuropathy was significantly more frequent in patients with coexisting HT and T1DM, most likely during the observed weight gain and glycogen deposition around nerve fibres[18]. A study by Gimenez-Perez et al. found that isolated AITD was associated with a lower incidence of kidney disease, while the co-occurrence of other AID elevated the incidence of ischaemic heart disease[8]. Both hyperthyroidism and hypothyroidism in several complex processes can lead to pre-renal and renal kidney damage by affecting renal blood flow, glomerular filtration rate (GFR), and renal tubular function[23]. Prinz et al. point to an increased risk of diabetic nephropathy in patients with T1DM and HT, although levothyroxine replacement therapy makes it possible to reverse this pathomechanism and demonstrates a nephroprotective effect[18]. Cardiovascular diseases are among the most significant complications of diabetes, including type 1[24]. While patients with autoimmune thyroid disorders co-occurring with T1DM did not have an increased risk of peripheral artery disease[8,24,25], the risk of developing atherosclerosis and ischaemic heart disease in this patient group is several times higher than in the general population[24]. Głowinska-Olszewska et al. found that even adolescents and young adults with T1DM and HT demonstrated a more unfavourable cardiovascular risk profile than comparators with isolated T1DM[24]. The study also showed higher levels of high-sensitivity C-reactive protein (hs-CRP) in this group of patients, which increased cardiovascular risk[24].

COELIAC DISEASE

The CD is a chronic multiorgan autoimmune disease in which genetically predisposed individuals develop small intestine damage due to gluten consumption. A family of storage proteins referred to as gluten, or prolamins, is naturally present in some grains like wheat, rye, barley, and spelt[26]. Under the influence of gluten, the production of specific antibodies [anti-tissue transglutaminase type 2 (anti-TG2), anti-gliadin (AGA), anti-endomysial (EMA), anti-deamidated gliadin peptides (anti-DGP)] and an autoimmune inflammatory reaction leading to villous atrophy of the small intestinal mucosa occur[26]. With a reported prevalence of 0.5–1% in the general population, CD is one of the most prevalent AID[26]. It can develop at any age, from early childhood to the geriatric population. However,

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recent cohort prospective studies have shown that most patients develop CD before the age of 10 years, with a female predominance[27].

The risk of CD in patients with T1DM is significantly higher than the population risk of developing the disease, and it varies from 1.9% to 10%[28–30]. When both disorders are present in the same patient, T1DM typically precedes CD. One of the largest multicentre multinational studies enrolling 52,721 young people with T1DM confirmed a higher risk of CD in children who have received a diagnosis of T1DM at a young age, particularly at <5 years old[28].

Similarly, the analysis of more than 9,000 patients with T1DM conducted by Vajravelu et al. found that CD incidence was greater with childhood-onset (<18 years) than with young adult-onset (≥18 years) diabetes[31].

Since 95% of patients with T1DM, and more than 98% of patients with CD, carry the human leukocyte antigen (HLA) class II genes DQ2 and DQ8, it has been determined that T1DM and CD share a common genetic origin[32]. High-risk HLA molecules bind specific gluten fragments or the islet self-antigen(s) and present them to antigen-responsive T lymphocytes. Intestinal enterocytes and/or the pancreatic β-cells are both destroyed by the autoimmune response in a pro-inflammatory environment[33]. Recent evidence, however, indicates that environmental or non-genetic variables play an essential role in the association of these disorders[34]. Accordingly, 75–86% of monozygotic twins have CD, while the proportion diminishes to 16–20% in dizygotic twins[35]. These environmental factors might include upper respiratory tract infections in young children in the first nine-month period[36]. Moreover, during a prospective observational birth cohort study among 6,605 children with a genetic predisposition to CD, higher gluten intake during the first five years of life was linked to an increased risk of CD[37].

Typical gastrointestinal symptoms of CD are due to malabsorption. Chronic diarrhoea, steatorrhea, abdominal pain, weight loss, and growth inhibition in children are often reported. Less common symptoms include recurrent aphthous stomatitis, loss of appetite, constipation, or vomiting. In non-classical CD, patients present without signs and symptoms of malabsorption, usually with one dominant clinical manifestation. Extraintestinal symptoms of the disease include anaemia, menstrual disorders, chronic fatigue, irritability, deterioration of bone structure, and others[38].

Patients with T1DM usually have a mild or asymptomatic course of CD, which often impedes early disease identification. The CD-DIET study in Canada included 1,298 adults and 1,089 children with T1DM without any CD symptoms who underwent serologic screening. Anti-TG2 were positive in 6.8% of adults and 4.7% of children, and the diagnosis was confirmed by biopsy in 4.2% and 2.6% of cases, respectively. Given the high prevalence of CD in patients with T1DM, and the fact that asymptomatic CD was 1.5-fold more common in adults than children, it seems necessary to conduct regular screening with a special vigilance in this group of patients[39].

The treatment of patients with co-morbidities frequently increases the risk of complications, causes therapeutic difficulties, and demands more vigilance. Craig et al. demonstrated lower height standard deviation (*SD*) in patients with CD. In addition, in their large population, fewer patients were overweight/obese, whereas glycaemic control was comparable[28]. The impairment of linear growth was also found in a study by Simmons et al. for both sexes. Children younger at CD onset remain shorter throughout childhood[40]. Furthermore, patients with both comorbidities are more likely to experience hypoglycaemic episodes and presumably develop diabetic retinopathy and nephropathy[41,42]. Fortunately, this risk might be expected to decrease after implementing the gluten-free diet[42].

Moreover, failure to adhere to a gluten-free diet has a notable significance for this group of patients, as it can result in poorer quality of life, lower general well-being, and worse diabetes control[43]. The group with the most significant difficulties in following dietary recommendations are asymptomatic patients during the CD diagnosis[43].

ADA 2023 guidelines recommend screening T1DM patients for CD by measuring the TG2 IgA level. At the same time, total serum IgA titres should be determined to exclude their deficiency, which occurs with a frequency of 0.2% in the general population[44]. In cases of IgA deficiency, TG2 IgG or anti-DGP should be measured. The screening should be repeated within two years of diabetes diagnosis and then again after five years. After that time, the measurement of the aforementioned antibodies should be considered in young patients with symptoms or a first-degree relative with CD[4].

It is essential to ensure that the patient eats gluten-containing products before testing for CD. According to the current European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines, if an anti-TG2 titre of >10 fold is found and if the patient's other independent blood sample was positive for EMA IgA, there is no requirement for a biopsy to diagnose CD[45].

The basis of treatment is exclusion of gluten-containing foods from the patient's diet. In patients with T1DM and CD, adherence to a gluten-free diet is linked to several favourable health outcomes. It is necessary to remember the need to include a clinical nutritionist in the care of patients with T1DM and CD due to the crucial role of diet in the daily life of individuals with these two comorbidities[4,45].

AUTOIMMUNE GASTRITIS AND PERNICIOUS ANAEMIA

T1DM co-occurs with AIG and PA in 0.3–5% of cases[12,46]. The pathomechanism of AIG includes atrophy of the mucosa, mainly in the corpus and the fundus of the stomach, manifested by the presence of the parietal cell antibodies (PCA) and intrinsic factor (IF)[47]. De Block et al. found that AIG affected 57% of PCA-positive and only 10% of PCA-negative patients[48]. PCA-positive individuals are more

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susceptible to developing AIG, iron deficiency anaemia, PA, intestinal metaplasia or enterochromaffin-like (ECL) hyperplasia[48]. PA develops at an advanced stage of gastritis, usually after an average of 20 years of disease duration[17,47]. Due to the progressive loss of the number of parietal cells, the production of IF and thus the absorption of vitamin B_{12} decreases; moreover, antibodies against the parietal cells block the formation of the vitamin B_{12}-IF junction[20,47]. In the study by De Block et al., evaluation of patients with T1DM and coexisting gastric autoimmunity indicated no significant differences in age, sex, duration of diabetes, HLA-DQ type, or association of positive TPOAb titres compared to patients without AIG[48]. However, Mäkimattila et al. found that patients with T1DM who developed AIG were older, had a longer duration of diabetes, and the diagnosis was made at a later age compared to patients with isolated T1DM[13]. A similar correlation with relative age and duration of diabetes has also been shown in paediatric patients. In the Kakleas et al. study, children who developed AIG were older at the time of diabetes diagnosis than children with isolated T1DM[3]. In addition, in the cited study involving 121 paediatric patients, AIG occurred in 5.2% of cases, and also differed in relation to gender, affecting 40% of boys and 60% of girls[3]. Patients with T1DM and a positive titre of PCA should be screened for AIG and PA[48]. Evaluation of PCA has to be done at the time of diagnosis of diabetes, then once a year for the next three years, followed by once every five years or more often if clinically indicated[49]. In children and adolescents, AIG is rarely symptomatic, so screening should be performed in each patient with iron deficiency, anaemia, AITD or age over 15 years[50]. In patients with T1DM, immunological risk factors associated with PCA antibodies include positive titres of anti-GAD and thyroid peroxidase[47]. Indeed, the GAD antigen is present in the pancreas and the gastric mucosa and submucosa, which indirectly stimulates hydrochloric acid production by the parietal cells[20]. PCA positivity and hypergastrinaemia were risk factors for AIG[48]. PCA-positive patients with AIG and hypergastrinaemia have an increased risk of preneoplastic gastric lesions – in the study by De Block et al. study, they were found in 26% of PCA-positive patients[48]. In patients with a high titre of anti-gastric antibodies and hypergastrinaemia, it is recommended to extend the diagnosis to gastroscopy with biopsy sampling for histopathological evaluation[20].

ADDISON'S DISEASE

Primary adrenal insufficiency (PAI), also known as AD, is a rare endocrine entity with a prevalence in the general population estimated at 93–140 per one million[51]. The disease can occur at any age, but it is usually diagnosed between the ages of 20 and 50 years, with a slight predominance in women. In developed countries, autoimmune PAI (APAI) accounts for approximately 80% of cases and is caused by the destruction of the adrenal cortex by cytotoxic T cells mediated by autoantibodies, usually against 21-hydroxylase or 17-hydroxylase[52]. The prevalence of APAI in patients with T1DM is 0.2–0.4%[53]. However, as many as 10.8–14.1% of patients with APAI also suffer from T1DM[53], and the risk of developing APAI in T1DM patients is approximately tenfold higher than in the general population[54]. The onset of T1DM usually precedes the diagnosis of APAI by several years[55].

PAI results in a deficiency of glucocorticosteroids, mineralocorticosteroids and androgens, and patients usually present with progressive weakness, lack of appetite, weight loss, orthostatic hypotension, and non-specific gastrointestinal symptoms (nausea, vomiting, abdominal pain, constipation or diarrhoea). Cortisol and aldosterone deficiencies lead to water and electrolyte imbalance, including hypovolaemia, hyponatraemia, hyperkalaemia, and increased plasma renin activity[52,56]. Cortisol deficiency also impairs gluconeogenesis, decreases glucose output from the liver, and increases insulin sensitivity with increased peripheral glucose utilisation, resulting in the risk of hypoglycaemia[57]. Due to the opposing effects of insulin and glucocorticoids on glucose homeostasis in patients with T1DM, hypoglycaemia is usually the most prominent and early feature of PAI[58]. Therefore, PAI should be considered in T1DM patients with unexplained and recurrent hypoglycaemic episodes and unexplained decrease in daily insulin requirement[58,59].

Hormonal tests in patients with PAI show reduced serum cortisol, aldosterone, dehydroepiandrosterone (DHEA), and increased plasma adrenocorticotropic hormone (ACTH) concentrations[52,56]. Basal cortisol and ACTH levels should be immediately assessed in patients with a clinical suspicion of PAI[52,56]. It has been postulated that moderately increased ACTH levels might be considered an early indicator of PAI, regardless of basal serum cortisol concentration, and help identify the individuals that should undergo a corticotrophin-stimulation test[60]. Chronically elevated concentrations of plasma ACTH might lead to skin hyperpigmentation, which in patients with T1DM could be suggestive and should be considered for APAI[52,56].

Early diagnosis of PAI and implementation of appropriate treatment in patients with T1DM is essential, especially since patients with these two concomitant conditions are at a higher risk of potentially life-threatening adrenal crisis[61,62], infections requiring hospitalisation, and numerous diabetic complications than patients with isolated T1DM[63]. Patients with the coexisting T1DM and APAI also have a fourfold higher risk of premature all-cause mortality than matched controls with T1DM alone, with diabetic and cardiovascular complications being the most common causes of death[63].

Although early detection of PAI in T1DM patients would potentially prevent increased morbidity and mortality in this group, no specific screening recommendations for PAI in T1DM exist; thus, physicians have to be aware of the warning signs that could prompt the diagnosis. It has been postulated to use 21-hydroxylase autoantibodies to

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screen for APAI at the time of T1DM diagnosis[64]; however, a negative result does not preclude their emergence and APAI development in the future[56,64]. Additionally, negative adrenal antibodies do not exclude APAI, since approximately 10% of T1DM patients with APAI are negative for 21-hydroxylase autoantibodies; on the other hand, approximately only 15% of T1DM patients who are positive for 21-hydroxylase autoantibodies have biochemical evidence of PAI[64]. In a nationwide registry study in Sweden in individuals with T1DM, four clinical factors were identified that were more common in patients before a diagnosis of APAI, including concomitant AITD, occurrence of severe infections, prescription of glucagon for hypoglycaemia, and diabetic retinopathy[65].

Treatment of PAI in patients with T1DM does not differ from the general principles and is based on chronic substitution with hydrocortisone and fludrocortisone; DHEA substitution might also be considered[52,56]. However, replacement therapy with insulin and glucocorticoids might be challenging, considering their opposing effects on glucose metabolism and the need to mimic their diurnal rhythm. It has been previously shown that patients with T1DM and PAI require higher preprandial but lower basal insulin doses when compared to patients with T1DM only[66]. Incorrectly adjusted substitution treatment also increases the risk of hypo- and hyperglycaemia, diabetic ketoacidosis, and adrenal crisis in individuals with T1DM and PAI[53]. In a nationwide observational cohort study in Sweden, patients with T1DM and PAI more commonly than those with T1DM alone were on antihypertensive treatment, which was considered as an indicator of even higher cardiovascular risk in patients with both diseases than T1DM alone, and speculated to be an effect of hypertension promotion by the hydrocortisone substitution regimen favouring glucocorticoid overreplacement[65]. Once-daily administration of dual-release hydrocortisone in patients with PAI, allowing for more physiological glucocorticoid substitution, might improve the outcomes of patients with concomitant T1DM[67].

VITILIGO

Vitiligo is a skin disorder affecting approximately 0.5–2% of the global population[68]. Due to the autoimmune process, melanocytes in the skin, hair, and mucous membranes are progressively destroyed or lose their function, leading to the appearance of delimited depigmentation of the skin. Although the disease may occur at any age, two major age-of-onset subgroups have been described: early-onset (mean 10.3 ± 5.6 years) and late-onset (mean 34.0 ± 14.5 years)[69].

While the aetiopathogenesis of the disease is not fully recognised, genetic and environmental factors may have a significant role in its occurrence. Several theories have been proposed for the pathogenesis of vitiligo, including autoimmune, neural, cytotoxic, and oxidative stress hypotheses[70]. Anti-melanocyte antibodies have been identified in a significant proportion of vitiligo patients, and their presence may positively correlate with the severity of the disease[71].

Vitiligo co-occurs with other AID in nearly 20% of patients[72], though there are studies that showed even higher rates. Accordingly, the incidence of vitiligo is also elevated in patients with T1DM, as it can affect 2.4% of patients[12]. Interestingly, studies have also shown a higher prevalence of vitiligo in patients with type 2 diabetes, which is explained by the fact that oxidative stress is involved in the pathogenesis of both diseases[73].

Vitiligo in a patient with T1DM may be considered a risk factor for other AID, especially AITD. The reported prevalence of positive thyroid antibodies is 34%[74] and vitiligo usually precedes AITD by many years[75]. Therefore, TPOAb should be screened initially, and TSH levels should be measured regularly, especially in patients with TPOAb at the initial screening.

Vitiligo is typically diagnosed clinically based on the presence of amelanotic, chalky-white macules with distinct margins in a typical distribution: periorificial region, lips, armpits, distal extremities, as well as in the groin and genital area.

There is no effective treatment for vitiligo. First-line treatment includes topical therapy with corticosteroids and/or calcineurin inhibitors. Second-line treatments include phototherapy [narrow-band ultraviolet B (NB-UVB) and psoralen plus UV-A (PUVA)] and systemic steroid treatment. Surgical grafting techniques may also be considered in some cases[76].

The presence of vitiligo in T1DM seems to have little effect on diabetes management. However, meta-analyses show that patients with vitiligo often suffer from a range of psychological problems, such as depression and anxiety. The occurrence of both diseases – significantly impairing the quality of life and predisposing to psychological disorders – will often require individual psychological care[76].

AUTOIMMUNE POLYGLANDULAR SYNDROME

APS is defined as a combination of at least two autoimmune-mediated disorders. Individual entities differ in the inheritance pattern, relationship with sex, and frequency of individual endocrinopathies and comorbidities[77–80]. T1DM is one of the most common endocrinopathies of the APS, and it is often the first disease to appear[80].

The major APS-1 components include mucocutaneous candidiasis, PAI and/or hypoparathyroidism. It is caused by autoimmune regulator gene (*AIRE*) mutations with an autosomal recessive inheritance pattern[77–80]. The disorder is rare, with a female-to-male ratio of 0.8–2.4; however, the prevalence of APS-1 is higher in certain populations, including Finns, Sardinians, and Iranian Jews[78,79]. Only about 12%

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Disease	Prevalence in general population	Prevalence in T1DM patients
Autoimmune thyroid disease	7.5% for Hashimoto's thyroiditis 1–1.5% for Graves' disease	17–30%
Coeliac disease	0.5–1%	1.9–10%
Autoimmune gastritis and pernicious anaemia	0.1–2%	0.3–5%
Addison's disease	0.01%	0.2–0.4%
Vitiligo	0.5–2%	2.4%

Tab. 1. Prevalence of selected autoimmune diseases in the general population compared to patients with T1DM[1–6]

of patients with APS-1 develop T1DM, and diabetes is typically a late complication compared to other comorbidities[77]. Concomitant components of APS-1 include ovarian failure in females and testicular failure in males, autoimmune gastritis, AITD, vitiligo, alopecia, autoimmune hepatitis, diabetes insipidus, hypophysitis, and other conditions. Typically, individuals present with 4–5 manifestations of the syndrome, but they may also develop fewer or even more of them[77–80].

The APS-2 is characterised by the T1DM, APAI, and AITD triad, with the annual incidence estimated at 1:20,000[80]. The syndrome occurs about three times more often in women than in men[81], with a peak prevalence at 20–40 years of age[77]. The inheritance pattern is autosomal, polygenic, and strongly associated with polymorphisms of the HLA genes and the environmental factors responsible for organ-specific damage. APS-2 disorders include CD, vitiligo, alopecia, myasthenia gravis, PA, autoimmune hepatitis, and other conditions. T1DM is a frequent component entity of APS-2 and often its first manifestation[78].

APS-3 includes the same spectrum of autoimmune-mediated endocrinopathies as APS-2 but without APAI[77–79]. APS-3 is the most frequent subtype of APS and contains approximately 41% of the possible endocrine component combinations. It is inherited in an autosomal dominant pattern with incomplete penetrance and, as in APS-2, it is strongly associated with polymorphisms of the HLA genes. T1DM is typically the first manifestation of APS-3 and usually develops at a very young age[79].

APS-4 is a very heterogeneous and less defined group of APS, and usually refers to clinical situations where the coexistence of AID does not fulfil the criteria of APS-1 to 3. As in APS-2 and 3, the development of an autoimmune reaction is associated with a genetically determined predisposition. The clinical picture depends on the syndrome components, but the most frequently described is the coincidence of T1DM and CD[79].

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is an extremely rare entity characterised by early-onset systemic autoimmunity in male children. It is caused by mutations in the *FOXP3* gene encoding forkhead box 3 protein – a transcription factor highly expressed in regulatory T cells. The generalised autoimmune process starts in the first months of life and leads to T1DM, an autoimmune enteropathy with intractable diarrhoea and malabsorption, and severe dermatitis. Some patients develop autoimmune nephritis, AITD, alopecia, autoimmune hepatitis, and various autoimmune cytopaenias.

	Polish Diabetes Association (Polskie Towarzystwo Diabetologiczne, PTD), 2023	American Diabetes Association (ADA), 2023	International Society for Pediatric and Adolescent Diabetes (ISPAD), 2022
Autoimmune thyroid disease	TSH concentrations and TPOAb to be determined in every patient with newly diagnosed T1DM and those who have not previously undergone tests to assess thyroid hormone function **For children and adolescents:** At the time of T1DM onset: TSH, fT4, TPOAb and TGAb (ultrasound in patients with positive antibodies and/or thyroid dysfunction), then every two years (depending on the doctor's decision): TSH and TPOAb, TGAb	Measurement of TSH, TPOAb and TGAb recommended soon after diagnosis and then every two years if thyroid antibodies are negative; more often if symptoms develop or thyroid antibodies are present	Measurement of TSH, TPOAb and TGAb recommended soon after diagnosis and then every two years in asymptomatic individuals and every year in individuals with positive antibodies and/or family history of ATD
Coeliac disease	In the absence of disease symptoms screening every two years	Screening by measurement of IgA tTG if total IgA is normal; IgG tTG and deamidated gliadin antibodies if IgA deficient soon after diagnosis and then within two years and then at five years after diagnosis; sooner if symptoms develop and/or family history is positive. Screening for IgA deficiency at the time of CD screening	Screening by measurement of IgA tTG or IgA EmA recommended during the initial year of diagnosis and at intervals of two to five years and more frequently if symptoms develop and/or family history is positive. Screening for IgA deficiency at the time of CD screening
Autoimmune gastritis, pernicious anaemia, Addison's disease	No recommendations available	No recommendations available. Careful vigilance for signs and symptoms of the diseases	No recommendations available. Careful vigilance for signs and symptoms of the diseases

Tab. 2. Summary of recommendations about screening in patients with selected autoimmune diseases[7–9]

The disorder is frequently fatal in the first few years of life[77,82,83] (Tabs. 1, 2).

SUMMARY

T1DM is an AID that often co-occurs with other autoimmune-mediated disorders, particularly AITD, CD, and autoimmune gastritis. The coexistence of T1DM and another AID significantly impacts the metabolic control of diabetes, the patient's quality of life, and the risk of developing diabetes-specific complications. Detailed recommendations regarding the screening for other AID in T1DM patients are under discussion. For some of them, there are specific standards, e.g. with the use of specific autoantibodies, and in the case of others, primarily due to their rarity, there are none. Physicians must maintain a high clinical suspicion of possible concomitant AID, especially in patients with unexplained worsening of diabetes control or hypoglycaemia, and implement proper management in order to prevent further complications and decrease the overall mortality. Further studies are required to define in detail the principles and the frequency of screening for other AID in T1DM patients.

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

Author contributions

Original concept of study: JS, ZZ, ŁD, PW. Collection, recording and/or compilation of data: JS, ZZ, ŁD. Analysis and interpretation of data: JS, ZZ, ŁD. Writing of manuscript: JS, ZZ, ŁD. Critical review of manuscript: JS, ZZ, ŁD, PW. Final approval of manuscript: JS, ZZ, ŁD, PW.

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