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## Autoimmune diseases in type 1 diabetes: Often overlooked?

It is frequently observed that type 1 diabetes mellitus, but also type 2 diabetes, can occur in combination with various other conditions, including endocrine disorders. Vascular diseases, autonomic neuropathies, or metabolic imbalances may lead to changes in endocrine function [1].

According to a 2019 study [2], patients with T1D have an increased risk of other autoimmune diseases, such as thyroid diseases and celiac disease, which may occur as comorbid conditions. Shared genetic factors and dysregulated immune mechanisms explain the coexistence of these autoimmune conditions.

The most common autoimmune thyroid disorders are Hashimoto's thyroiditis (hypothyroidism) and Graves' disease (hyperthyroidism). These chronic inflammatory thyroid disorders are caused by dysregulation of the specific immune response involving B and T lymphocytes. In Hashimoto's thyroiditis, anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies can typically be detected, while Graves' disease is associated with TSH receptor antibodies.

According to [1], certain autoimmune diseases tend to occur more frequently in women with type 1 diabetes. These include autoimmune thyroid disorders such as Graves' hyperthyroidism but also hypothyroidism caused by autoimmune thyroiditis.

Table 1 lists selected endocrine autoimmune diseases that may occur in combination with type 1 diabetes.



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Table 1: Endocrine autoimmune diseases in combination with type 1 diabetes

| Disease | Incidence | Female/Male Ratio | Association with T1D |
|---|---|---|---|
| **Hashimoto's thyroiditis (HT)** | Estimated at 3–6 cases per 10,000/year (2020) [3] | Occurs nine times more often in women, especially ages 30–50 [3] | HT is 3–5 times more common in T1D patients than in individuals without other immunological disorders [1] |
| **Graves' disease (GD)** | About 20 cases per 100,000/year in Western countries [4] | Five- to tenfold higher incidence in women; peak between ages 50–60 [1] | Up to 57% of untreated GD patients exhibit impaired glucose tolerance; 2–3.3% have diabetes [1] |
| **Autoimmune adrenalitis (Addison's disease; AD)** | Approx. 4–6 cases per 1 million/year in Europe [5] | Slightly more common in women (OR 1.2) [5] | 12% of women with AD also developed T1D [5] |
| **Autoimmune parathyroiditis (AP)** | Prevalence approx. 1:80,000 [6] | No significant sex differences in calcium or PTH levels [7] | 80–85% of patients with polyglandular autoimmune syndrome develop both T1D and AP [8] |

Other autoimmune diseases that may occur in combination with T1D are listed in Table 2 and briefly summarized below.

**Hypophysitis:** According to [9], the true annual incidence is difficult to determine, with older estimates suggesting 1 in 9 million. Improved diagnostics and imaging have increased the reported incidence.

**Autoimmune hepatitis (AIH):** AIH is an inflammatory liver disease caused by a T-cell-mediated immune reaction against hepatic antigens [10]. Women are affected four times more often than men. AIH often progresses chronically and may lead to fibrosis and cirrhosis if untreated. AIH is more common in people with T1D and may require more intensive diabetes management [11].

**Chronic atrophic gastritis (CAG):** CAG is considered a precursor of gastric cancer. It is linked to antibodies against parietal cells. Due to often asymptomatic progression, incidence data are limited. In patients without prior H. pylori infection, incidence is low [12].



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**Gluten-sensitive enteropathy (Celiac disease):** Celiac disease is an autoimmune disorder characterized by antibodies against transglutaminase. Untreated cases increase morbidity and mortality [13]. In Germany, the prevalence among children and adolescents was 0.9% in a 2003 study. Women have a higher risk of undiagnosed celiac disease than men.

**Secondary vasculitis:** Secondary vasculitis may be triggered by autoimmune diseases, infections, or medications [14]. Rheumatoid vasculitis may occur in combination with T1D (author's note).

Table 2: Other autoimmune diseases associated with T1D

| Disease | Incidence/Prevalence | Female/Male Ratio | Association with T1D |
|---|---|---|---|
| **Hypophysitis** | Estimated 1 case per 9 million/year (2005) [9] | IgG4-related form more common in men (2:1) [15] | No established data |
| **Autoimmune hepatitis (AIH)** | 0.2–1.2 new cases per 100,000/year [11] | 4:1 (peak 10–30 years) [10] | Prevalence higher in T1D patients (44.8/100,000) [11] |
| **Atrophic gastritis (CAG)** | Incidence up to 11%/year; <1% without H. pylori [16] | Increases with age (0.5% at 50–54 years; 2.1% at 70–74 years) [13] | Found in 4.3% of T1D patients [2] |
| **Celiac disease** | Prevalence approx. 0.9% among children in Germany [13] | Higher risk in women [17] | Prevalence 4.5% in T1D patients [2] |

Polyglandular autoimmunity refers to the special case in which multiple hormone glands are affected by a disease caused by the formation of antibodies directed against the body's own tissues. This is therefore classified as an autoimmune disease. There are several types of polyglandular, also known as pluriglandular, autoimmunity.


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**Autoimmune Polyendocrine Syndrome (APS):** Autoimmune polyendocrine syndrome, abbreviated as APS, refers to a group of autoimmune diseases that often occur simultaneously and primarily affect endocrine glands, but can also involve other tissues, as described in source [18]. According to source [19], APS type 1 is extremely rare (1 case per 100,000 individuals) and is caused by a monogenic mutation. Clinically, it usually appears in childhood with a typical sequential onset of mucocutaneous candidiasis, hypoparathyroidism, and Addison's disease.

APS is defined by the impairment of at least two endocrine organs due to autoimmune reactions, and several years may pass between the appearance of individual symptoms [19].

**Classification of APS types:** According to source [18], different classifications of APS types are described in the literature (see Table 3). Most commonly, two main types are distinguished, although some research groups further divide APS type 2 into types 3 and 4. While type 1 is monogenetically inherited and occurs more frequently in children, type 2 (including types 3 and 4) represents a syndrome with familial clustering in adults.

**Table 3: (modified from [19]): Forms of Polyglandular Autoimmune Syndromes:**
AIE = Autoimmune Endocrinopathy
APECED = Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy Syndrome

| APS Type | Definition | Incidence | Sex Distribution | Association with T1D |
|---|---|---|---|---|
| **Type 1 (juvenile APS)** | APECED syndrome | 1:100.000 | 4:3 | < 20 % |
| **Type 2 (adult APS)** | Addison's disease + autoimmune endocrinopathy | 1:20.000 | 3:1 | 50–60 % |
| **Type 3 (adult APS)** | Autoimmune endocrinopathy + autoimmune thyroid disease (no Addison's) | | | |
| **Type 4 (adult APS)** | Any combination of ≥2 autoimmune endocrinopathies (not APS 1–3) | | | |
| * Synonym: Schmidt syndrome | | | | |



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Regular follow-up examinations are recommended for all patients at risk for APS 1 [19]. Since some disease components can progress rapidly during acute clinical episodes, clinical evaluations should be performed at least every six months. If autoantibodies are detected, additional functional tests—such as an ACTH stimulation test—should be conducted as needed.

APS typically develops sequentially, with type 1 diabetes usually appearing first. Studies have shown that over 50% of individuals with type 1 diabetes have additional pathological autoantibody titers, and 31% develop at least one other treatable autoimmune endocrinopathy [19]. The most common condition to develop after diabetes is autoimmune thyroid disease, with a prevalence of 3.6% within one year, making it the most frequent form of APS in adults.

**Conclusion for Clinical Practice**

Due to the comorbidities of autoimmune diseases and type 1 diabetes (T1D), autoantibody screening is recommended at initial diagnosis—particularly Anti-TPO antibodies, TRAb, adrenal antibodies, transglutaminase antibodies, and parietal cell antibodies. If additional symptoms arise, such as joint pain, gastrointestinal complaints, etc., other autoimmune diseases should also be considered, and appropriate diagnostic tests should be initiated.

Because diabetes mellitus and thyroid dysfunctions often occur together (either simultaneously or at different times), thyroid function should be checked regularly—at least once per year—as well as in cases of unexplained deterioration of metabolic control. This ensures timely and appropriate treatment to help stabilize metabolic processes.

**Keywords:** Hypoparathyroidism – Addison's disease – Graves' disease – Hashimoto's disease – Rheumatoid arthritis – Autoantibodies – Autoimmune disease – Type 1 diabetes mellitus (T1D) – APS

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## Biography

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