



REVIEW

# Recent advances in understanding autoimmune thyroid disease: the tallest tree in the forest of polyautoimmunity [version 1; referees: 2 approved]

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**Abstract**

Autoimmune thyroid disease (AITD) is often observed together with other autoimmune diseases. The coexistence of two or more autoimmune diseases in the same patient is referred to as polyautoimmunity, and AITD is the autoimmune disease most frequently involved. The occurrence of polyautoimmunity has led to the hypothesis that the affected patients suffer from a generalized dysregulation of their immune system. The present review summarizes recent discoveries unravelling the immunological mechanisms involved in autoimmunity, ranging from natural autoimmunity to disease-specific autoimmunity. Furthermore, the clinical grounds for considering AITD in a setting of polyautoimmunity are explored. A better understanding of these may pave the way for designing new treatment modalities targeting the underlying immune dysregulation when AITD appears in the context of polyautoimmunity.

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## Introduction

Autoimmune thyroid diseases (AITDs), comprising the two main entities Hashimoto's thyroiditis (HT) and Graves' disease (GD), are the most common autoimmune diseases<sup>1</sup> and are often observed together with other autoimmune diseases. The occurrence of two or more diseases in the same patient is often referred to as polyautoimmunity<sup>2</sup>. This has led to the hypothesis that many patients with autoimmune disease, in general, suffer from an underlying dysfunction of critical mechanisms ensuring self-tolerance. The present review examines recent advances in the understanding of immunological aspects involved in autoimmunity, ranging from physiological to disease-specific autoimmunity, and explores the clinical grounds for considering thyroid autoimmunity in a setting of polyautoimmunity.

## Immunological aspects of polyautoimmunity

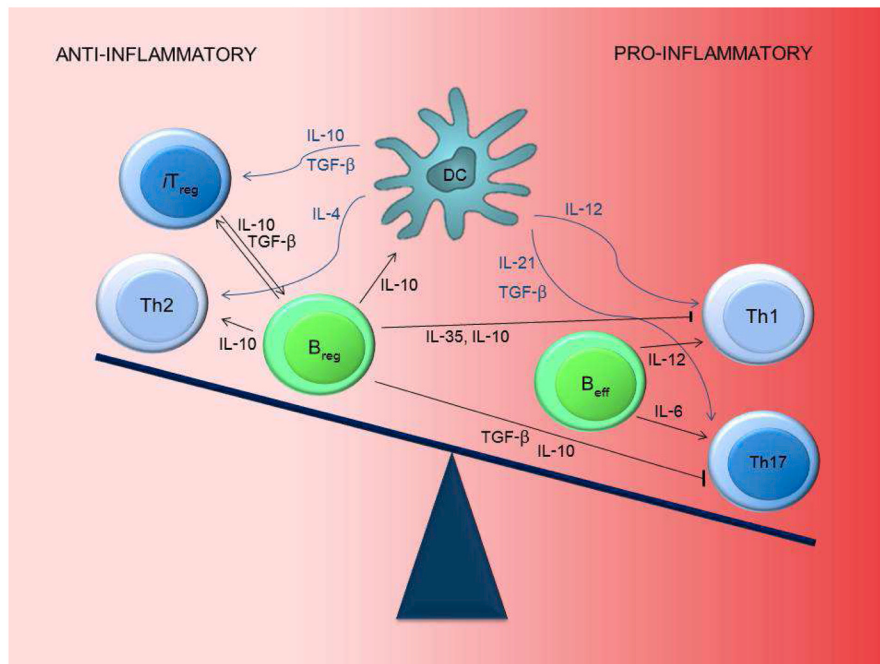
### Natural polyautoimmunity

At the beginning of the 20th century, Paul Ehrlich demonstrated that animals do not produce antibodies against their own red blood cells and coined the term "horror autotoxicus" for the immune system's reaction with the body's own constituents<sup>3,4</sup>. At the same time, the normal occurrence of autoantibodies against spermatozoa was demonstrated<sup>5</sup>. Since then, many studies have shown the existence of autoantibodies in healthy animals and humans, referred to as natural autoantibodies<sup>6,7</sup>. In general, natural autoantibodies show broad reactivity against more self- and non-self-antigens and are of the IgM isotype<sup>6,8</sup>, whereas disease-associated autoantibodies are of the IgG isotype and bind specific self-antigens with high affinity<sup>9,10</sup>. At least in mice, the subset of B cells producing natural

autoantibodies appears to be positively selected for self-reactivity in the bone marrow<sup>11</sup>. Although B cells and T cells binding to "self" with high affinity are negatively selected, self-reactive lymphocytes with low-affinity receptors are allowed to escape and enter the circulation but often without harmful consequences<sup>12,13</sup>. Thus, natural autoantibodies may serve a role in the clearance of aging cells and cells with tumor potential and may also exert anti-inflammatory control over B cells and T cells<sup>14,15</sup>. Natural autoimmunity should therefore be distinguished from disease-associated autoimmunity.

### Loss of self-tolerance

Autoimmune disease is preceded by loss of immunological self-tolerance, which may occur at the central level (during the selection processes described above) or in the periphery. The adaptive immune system's T cells and B cells usually keep the balance between reacting aptly toward foreign antigens and avoiding attack on "self". Both T cells and B cells contain subsets of regulatory cells with an immunoregulatory cytokine profile on the one hand and effector cells that produce antibodies or secrete pro-inflammatory cytokines on the other (Figure 1). Thus, the traditional view of a T helper type 1 (Th1)/Th2 dichotomy has been abandoned since it became clear that CD4<sup>+</sup> effector T cells can differentiate into several subsets of Th cells which stimulate different parts of the immune system: for example, Th1 cells stimulate cellular immunity and the production of opsonizing antibodies, Th2 cells stimulate IgE production, and Th17 cells stimulate neutrophils. Th1 cells and Th17 cells have been shown to play detrimental roles in many autoimmune diseases, including HT and GD<sup>16,17</sup>. Furthermore, Th17 cells have been associated with chronic



**Figure 1. B-cell and T-cell subsets controlling autoimmunity.** Peripheral self-tolerance is ensured by regulatory B cells and T cells. Autoimmunity (loss of self-tolerance) is considered to be due to a shift in favor of pro-inflammatory effector cells. B<sub>eff</sub>, effector B cells; B<sub>reg</sub>, regulatory B cells; DC, dendritic cell; IL, interleukin; iT<sub>reg</sub>, induced regulatory T cells; TGF-β, transforming growth factor beta; Th<sub>1,2,17</sub>, effector CD4<sup>+</sup> T-cell subsets with different cytokine profiles.

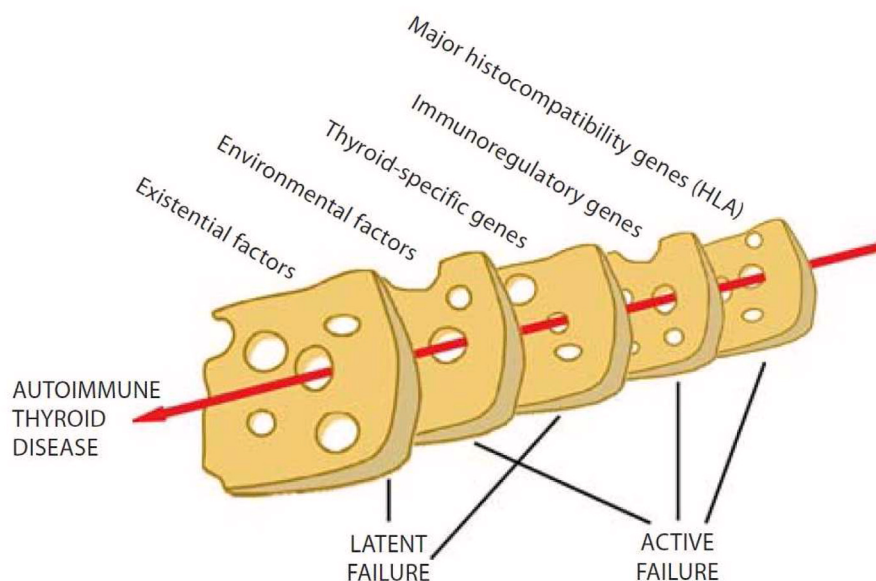
inflammation and autoimmune diseases such as systemic lupus erythematosus, Sjögren's syndrome, and systemic sclerosis<sup>18</sup>.

Regulatory T cells (Tregs) are primarily responsible for maintaining self-tolerance, and a protective role of Tregs has been demonstrated in several animal models of autoimmune diseases<sup>19,20</sup>. A subset of Tregs known as natural Tregs (nTregs) leave the thymus as fully differentiated cells, whereas another subset, inducible Tregs (iTregs), can be induced from naïve Th0 cells<sup>21</sup>. Both subsets are characterized by the expression of the transcription factor forkhead box protein 3 (FOXP3) and mediate their action in part via the secretion of interleukin-10 (IL-10) and transforming growth factor beta (TGF- $\beta$ )<sup>22</sup> and in part by mechanisms involving cell-to-cell contact<sup>23</sup>. Loss of peripheral self-tolerance is considered to be the result of an overweight of Th17 cell response as compared with induced regulatory Th10 cell response<sup>18</sup>. FOXP3 is involved in the peripheral self-tolerance processes by promoting the development of Tregs while inhibiting the differentiation of Th17 cells<sup>21</sup>. Mutations of the *Foxp3* gene can cause the immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, an early-onset, life-threatening autoimmunity characterized by substantial polyautoimmunity and often death within two years of birth<sup>24</sup>. Under less severe circumstances, overexpression of FOXP3 $\Delta$ 2, a splice variant of FOXP3 lacking exon 2<sup>25</sup>, may be associated with a shift toward a Th17 response, thereby increasing autoantibody production, as shown in a recent study of patients with HT<sup>26</sup>. Accordingly, a skewed balance between Th17 cells and Tregs<sup>18,21,26</sup> as well as dysfunctional Tregs<sup>19</sup> have been demonstrated in autoimmune disease in humans. A shift between Th10 and Th17 cells may occur according to the cytokine milieu in the microenvironment<sup>18,27</sup>. Recently, regulatory B cells (Bregs) have received much attention as inhibitors of inflammatory and autoimmune responses by the production of

regulatory cytokines (primarily IL-10)<sup>18</sup>. Another factor that may contribute to the development of autoimmune disease is therefore a cytokine expression dominated by effector B cells rather than by Bregs. Thus, both Tregs and Bregs contribute to the maintenance of peripheral tolerance (Figure 1).

### Development of autoimmune disease

The transition from natural to clinically manifesting autoimmunity relies on an interplay between genetic predispositions and environmental events, as depicted in Weetman's "Swiss cheese model" on AITD (Figure 2)<sup>28</sup>. Most autoimmune diseases are associated with specific variants of the human leukocyte antigen (*HLA*) genes. Several other genetic polymorphisms have been associated with autoimmune diseases, particularly some located at the genes encoding cytotoxic T lymphocyte-associated 4 (CTLA-4) and the protein tyrosine phosphatase, non-receptor type 22 (PTPN22)<sup>29</sup>. Each of these loci encodes molecules involved in the regulation of T cells. In particular, two rare syndromes illustrate the importance of T cells in maintaining self-tolerance: the first, autoimmune polyglandular syndrome type I (APS 1, also called APECED), is caused by defects in the autoimmune regulator (*AIRE*) gene that mediates the induction of T-cell self-tolerance in the thymus<sup>30</sup>. In patients with APS 1, multiple endocrine glands are dysfunctional. The second, FOXP3 deficiency, is associated with the IPEX syndrome, as mentioned above. Whereas APS 1 and IPEX syndrome are caused by mutation of a single gene, most cases of autoimmunity are likely the result of a broad range of genetic predispositions and environmental factors resulting in an imbalance of the peripheral self-tolerance mechanisms sustained by Tregs and Bregs (Figure 1)<sup>18</sup>. Thus, genetic polymorphisms in self-antigens, cytokines, estrogen receptors, and adhesion molecules have also been linked to the development of autoimmune disease<sup>28,31–36</sup>, as have genes coding for apoptotic processes<sup>37</sup>.



**Figure 2. Etiology of thyroid autoimmunity.** The development of autoimmune thyroid disease is a result of multiple events—a "Swiss cheese model". Figure reproduced with kind permission from Weetman<sup>28</sup>. HLA, human leukocyte antigen.

In addition to genetic variation, both post-transcriptional and post-translational events may contribute to the development of autoimmunity. Thus, translation of mRNA into protein may be regulated by binding of RNA-binding protein and microRNAs, and alternative splicing of mRNA may influence the functionality of encoded proteins<sup>38</sup>. As mentioned above, certain splice variants of FOXP3 mRNA have been associated with autoimmune disease, including HT<sup>26,39,40</sup>. An example of post-translational modification that enhances the immunogenicity of self-proteins is the conversion of arginine residues into citrulline residues, which has a major impact on autoantibody formation in rheumatoid arthritis<sup>41</sup>.

Several environmental factors may trigger autoimmune disease in genetically predisposed individuals, including bacterial and viral infections, cigarette smoking, maternal-fetal microchimerism<sup>42,43</sup>, and exposure to chemical compounds (flame retardants and phthalates)<sup>44</sup>, to mention but a few. Finally, being female predisposes to many autoimmune diseases, which may relate to hormonal factors and to X-chromosome inactivation patterns<sup>45,46</sup>.

### Autoimmune thyroid disease

AITD is increasingly viewed as a continuum not only including distinct disease entities—that is, HT, GD, subacute thyroiditis, primary myxedema, and Graves' orbitopathy (GO)—but covering a spectrum of diseases affecting the thyroid gland. However, in most thyroid research and in clinical practice, the two main entities of AITD remain as GD and HT with typically opposing main clinical manifestations: hyperthyroidism and hypothyroidism, respectively. In line with a more flexible view of AITD, both HT and GD are heterogeneous and can cause both hyperthyroidism and hypothyroidism<sup>47</sup>, even alternating between one form and the other<sup>48</sup>. GD and HT are among the most common autoimmune diseases in Western countries<sup>49</sup>. The pathogenesis is complex with a wide range of predisposing environmental, endogenous, and genetic factors, as described above and specified in relation to AITD in [Box 1](#)<sup>45,46,50–52</sup>.

HT is characterized by a direct T-cell attack on the thyroid gland, leading to thyroiditis and subsequent exposure of thyroid antigens (thyroid peroxidase and thyroglobulin) against which antibodies are then produced. Thyroglobulin antibodies (TgAbs) and thyroid peroxidase antibodies (TPOAbs) are commonly associated with HT with a destructive pattern and are considered diagnostic for this disease. In any iodine-sufficient population, however, the prevalence of TPOAbs and TgAbs is much higher than that of clinical disease, amounting to approximately 15–25%, with the highest prevalence in females and increasing with age<sup>53</sup>. GD is also primarily caused by a T-cell abnormality, but the hyperthyroidism associated with the disease is caused by the production of the pathognomonic thyrotropin receptor autoantibodies (TRAbs). The stimulating effect of TRAbs on thyrocytes probably has an influence on the formation of TgAbs and TPOAbs as well<sup>54</sup>. GD (and less commonly HT) can be complicated by GO, an autoimmune reaction in the orbita causing fibroadipose tissue and extraocular muscles to increase in size with a risk of permanent damage to the optic nerve. Shared antigens between the thyroid and orbita have been suspected to be the target of the autoimmune response, and TRAbs are likely to play a part in the pathogenesis. A general inflammatory cytokine profile

#### Box 1. Risk factors for autoimmune thyroid disease

##### Environmental

- Iodine consumption
- Smoking (possibly protective)
- Radiation
- Drugs (including biologic agents)
- Alcohol consumption (protective)
- Pollutants
- Selenium? Vitamin D?
- Infections (*Yersinia enterocolitica*)?
- Improved hygiene?

##### Endogenous

- Female sex
- Parity
- Aging
- Stress hormones
- Fetal microchimerism

##### Genetic

- Chromosome abnormalities
- Human leukocyte antigen types?
- Single-nucleotide polymorphisms?

(mainly Th1-driven) and autoimmune reactions toward the insulin-like growth factor 1 receptor (IGF-1R) have been demonstrated as well<sup>55</sup>.

### Polyautoimmune disease

Occasionally, patients suffer from more than one well-defined autoimmune disease. In the 1950s, it was recognized that certain “shared threads” characterized autoimmune diseases<sup>56,57</sup>, a notion which has since been the subject of much debate and research. Many terms have been suggested for such conditions: polyautoimmunity<sup>2,58</sup>, autoimmune diathesis<sup>57</sup>, autoimmune tautology<sup>59</sup>, or, in the case of three or more coexisting autoimmune diseases, multiple autoimmune syndromes<sup>60</sup>. Lack of a common terminology challenges any comprehensive literature search and review. In the following, the term “polyautoimmunity” is used to describe the coexistence of two or more autoimmune diseases in the same patient.

Several endocrine syndromes including more than one autoimmune disease have been described (a sample of them is illustrated in [Table 1](#)<sup>61–64</sup>). In polyglandular autoimmune syndrome type 2, Addison's disease occurs with AITD or type 1 diabetes (as well as with other autoimmune presentations)<sup>61</sup>. Such syndromes or classified clusters are rare in contrast to the presence of multiple autoantibodies (independent of clinical diagnoses) in patients with autoimmune disease. AITD, being the most common, is prevalent in most polyautoimmune syndromes and cases. The following sections describe the clinical findings related to thyroid autoimmunity in association with other autoimmunity.

**Table 1. Polyautoimmune endocrine syndromes including thyroid disease.**

Clusters	Proposed pathogenic mechanism
Autoimmune polyglandular syndromes <sup>61</sup>	
Type I (autoimmune polyglandular syndrome type I or Whitaker syndrome): mucosal and cutaneous <i>Candida</i> infections, Addison's disease, hyposplenism, hypoparathyroidism, and multiple autoimmune presentations (that is, hypothyroidism, hypogonadism, vitiligo, alopecia, pernicious anemia, and chronic autoimmune hepatitis)	Mutation of autoimmune regulator ( <i>AIRE</i> ) gene involved in central tolerance development. Phenotype possibly affected by human leukocyte antigen (HLA) subtypes <sup>62</sup> .
Type II (Schmidt's syndrome): Addison's disease and hypothyroidism or type 1A diabetes as well as pernicious anemia, primary hypogonadism, vitiligo, celiac disease, and myasthenia gravis (by some further classified in types III and IV according to specific entities above)	Polygenetic with increased risk of disease linked to specific HLA-DR and HLA-DQ genotypes <sup>63</sup>
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome <sup>24</sup> Immune dysfunction, enteropathy, dermatitis, autoimmune endocrinopathies (often type 1 diabetes and autoimmune thyroid disease), autoimmune skin diseases (that is, bullous pemphigoid), and multiple organ involvement	Mutation of <i>FOXP3</i> gene on the X chromosome
Multiple autoimmune syndromes <sup>60</sup>	
Type I: myasthenia gravis, thymoma, polymyositis, and giant cell myocarditis	
Type II: Sjögren's syndrome, rheumatoid arthritis, primary biliary cirrhosis, scleroderma, and autoimmune thyroid disorders	
Type III: autoimmune thyroid disease, myasthenia and/or thymoma, Sjögren's syndrome, pernicious anemia, idiopathic thrombocytopenic purpura, Addison's disease, insulin-dependent diabetes, vitiligo, autoimmune hemolytic anemia, and systemic lupus erythematosus	Genetic predisposition, with phenotype HLA B8 and/or DR3 or DR5 seeming to be an important factor
Thyrogastric cluster <sup>64</sup> Autoimmune thyroiditis, chronic gastritis/pernicious anemia, and autoimmune adrenalitis (Addison's)	Polygenetic
Lupus-associated cluster <sup>64</sup> Autoimmune hemolytic anemia, immune thrombocytopenia, systemic lupus erythematosus, rheumatoid arthritis, autoimmune hepatitis, and Sjögren's syndrome	Polygenetic
Trisomy 21 and Turner syndrome <sup>64</sup> Chronic thyroiditis, type 1A diabetes, and others	Chromosomal abnormalities
Kearns-Sayre syndrome <sup>64</sup> External ophthalmoplegia, retinal degeneration, diabetes, thyroiditis, and hypoparathyroidism	Mitochondrial myopathy

## Thyroid autoimmunity in association with polyautoimmunity

### Thyroid autoimmunity in other autoimmune disease

It is beyond the scope of this review to cover the numerous case reports describing polyautoimmunity. Instead, the present review will focus on clinical studies on polyautoimmunity involving AITD. In many studies, no distinction has been made between the various clinical phenotypes of AITD, and TgAbs, TPOAbs, and even TRAbs are often just referred to as "thyroid autoantibodies", making reported percentages indicative only.

In a Colombian study<sup>2</sup>, patterns of clustering were investigated among 1,083 patients. The patients had systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, or multiple sclerosis. AITD was the most prevalent disease, coexisting with systemic sclerosis in 23% of cases, rheumatoid arthritis in 21% of cases, systemic lupus erythematosus in 18% of cases, and multiple sclerosis in 9%<sup>2</sup>. No control group was provided to substantiate the findings. Among 479 patients with primary Sjögren's syndrome, Zeher *et al.* found 21% with AITD<sup>65</sup>. Another study from the same group showed that HT was significantly more prevalent than GD

in patients with mixed connective tissue disease, rheumatoid arthritis, and Sjögren's syndrome and that both AITDs were much more prevalent in such patients than in the background population<sup>66</sup>. A total of 8.2% of investigated patients with the investigated systemic autoimmune diseases had AITD based on clinical evaluation, imaging, and fine needle aspiration cytology<sup>66</sup>.

A few studies of autoantibody prevalence have included healthy controls. Nakamura *et al.*<sup>67</sup> found significant increases in TgAb and TPOAb positivity in all investigated autoimmune diseases compared with healthy controls: up to 50% in type 1 diabetes, 55% in autoimmune liver disease, 26% in myasthenia gravis, and 34% in connective tissue diseases<sup>67</sup>. Only patients with type 1 diabetes had TRABs more often than healthy controls (20% versus 0%,  $P < 0.01$ ). Interestingly, Liao *et al.*<sup>68</sup> found no significant difference in thyroid autoantibody positivity between 1,290 patients with rheumatoid arthritis and 1,236 controls without rheumatic disease (TPOAbs 15.6% versus 15.9%, TgAbs 1.1% versus 0.7%,  $P > 0.05$ )<sup>68</sup>. We have previously found TPOAbs in 5% of patients with rheumatoid arthritis, 19% with type 1 diabetes mellitus, 11% with Sjögren's syndrome, 56% with pernicious anemia, and 22% with primary biliary cirrhosis compared with 98% with HT and 7% in healthy controls, which is in keeping with the above-mentioned increased risk of autoimmune disease and not only positivity for autoantibody<sup>69</sup>.

### Non-thyroid autoantibodies and other autoimmune disease in autoimmune thyroid disease

Few studies have investigated the prevalence of non-thyroid autoantibodies or other autoimmune diseases in patients with AITD. In a recently published prospective study, 3,069 patients with chronic AITD were compared with 1,023 patients with non-toxic nodular goiter and 1,023 healthy controls<sup>70</sup>. Diagnosis of autoimmune disease was confirmed by a specialist according to scientific societies' criteria. Several of the concurrent autoimmune diseases were significantly more prevalent in patients with AITD than in the healthy controls. However, only three concurrent diseases had a prevalence of more than 2% in the AITD group: chronic autoimmune gastritis, vitiligo, and rheumatoid arthritis. Among observed clusters of disease, AITD together with chronic autoimmune gastritis and vitiligo formed a cluster with a significantly increased prevalence in the group of patients with AITD (12 patients versus 0 in other groups,  $P = 0.02$ )<sup>70</sup>.

In a Japanese population of patients with AITD, anti-glutamic acid decarboxylase antibodies were the most prevalent non-thyroid autoantibodies, being present in 6.4% of GD and in 4.6% of patients with HT<sup>67</sup>, thus confirming historical links between insulin antibodies and thyroid autoimmunity<sup>71</sup>. In a study of more than 3,000 UK patients with AITD, there was a significantly increased relative risk of any other autoimmune disease screened for compared with the background population<sup>72</sup>. Thus, 14.3% of the 495 patients with HT and 9.7% with GD had at least one other autoimmune disease, mainly type 1 diabetes, rheumatoid arthritis, and pernicious anemia. Wiebolt *et al.* investigated 359 patients with HT and 523 with GD and found differing patterns of autoantibody clustering in the two diseases<sup>73</sup>. Thus, adrenal autoimmunity combined with beta-cell or gastric autoimmunity was more common in patients with HT compared with patients with GD<sup>73</sup>.

### Epidemiological studies

Lack of power in clinical studies is made up for in epidemiologic studies. Eaton *et al.* included data from more than 5 million Danes from hospital registries to investigate the prevalence of 31 specified autoimmune diseases (based on the International Classification of Diseases 10th Revision (ICD10) classification system)<sup>74,75</sup>. Although data were limited to that of specialized care, the estimated lifetime prevalence of any autoimmune disease was 5.3%, and AITD most often coexisted with adrenal disease (odds ratio (OR) 12.9), alopecia areata (OR 11.4), vitiligo (OR 7.9), and pernicious anemia (OR 5.6)<sup>75</sup>. However, compared with connective tissue diseases in particular, AITD showed limited overlap with other autoimmune diseases. As many patients with autoimmune disease are handled in general practice, a British study used the United Kingdom General Practice Research Database to study the intra-individual risk of polyautoimmunity<sup>76</sup>. Along with large numbers of patients with insulin-dependent diabetes mellitus, rheumatoid arthritis, and multiple sclerosis, 26,198 patients with AITD were included. Patients with either AITD or rheumatoid arthritis were at risk of developing the other disease (sex-specific standardized incidence rate of 130.4–162.0)<sup>76</sup>. The risk of patients with type 1 diabetes having AITD was increased significantly in comparison with the background population having AITD; with a prevalence six times higher in males and a prevalence four times higher in females. This is in keeping with at least one previous cohort study, where patients with two autoimmune diseases, and thus probably stronger influence of genetic than environmental or other inherent factors, seemed to show a diminished or even abolished female preponderance of autoimmune diseases that is otherwise observed in the general population<sup>77</sup>. Thus, the *a priori* likelihood of contracting a second autoimmune disease is higher in males than in females with one autoimmune disease, which should be taken into account when managing male patients with AITD. Despite many inherent limitations, epidemiological studies provide further evidence of an increased risk of polyautoimmunity in patients with AITD. Without proving causality, the association between AITD and other autoimmune diseases seems well substantiated and with no strict distinction between organ-specific and non-organ-specific autoimmune disease.

### Clinical consequences of polyautoimmunity in thyroid autoimmunity

#### Clinical impact of (poly)autoimmunity

The chronic nature of autoimmune disease implies high socioeconomic costs as well as a profound impact on the patient's health and well-being<sup>78</sup>. The occurrence of polyautoimmunity rather than an isolated autoimmune disease may greatly affect prognosis. In a Dutch study, TPOAb positivity in patients with rheumatoid arthritis was predictive of disease activity—measured by the Disease Activity Score using 28 joint counts (DAS28)—and of increased carotid intima-media thickness at a 2-year follow-up<sup>79</sup>. The latter finding may indicate an increased risk of cardiovascular disease in patients with polyautoimmunity in accordance with the well-established association between increased inflammation and risk of cardiovascular disease<sup>80,81</sup>. In studies of reproductive failure, especially autoantibodies involved in the anti-phospholipid syndrome (that is, anti-cardiolipin antibodies)<sup>82</sup> but also thyroid autoantibodies<sup>83,84</sup> have been associated with worsened pregnancy

outcomes. In a study by Iijima *et al.*<sup>85</sup>, several autoantibodies were analyzed, and women with autoantibodies against one or more self-antigens had a significantly increased risk of miscarriage. However, only 5% of all women (25.8% of autoantibody-positive women) had multiple autoantibodies<sup>85</sup>. In women with recurrent pregnancy loss, a thorough examination of possible polyautoimmune etiology is therefore warranted, and immunotherapy appears to be beneficial<sup>86</sup>.

Few studies indicate an impact of an underlying immunological tolerance breach rather than thyroid dysfunction on the symptomatology involved in AITD. Abnormal brain perfusion in patients with euthyroid HT compared with controls has led to a hypothesis of an autoimmune component in decreased vascularization, possibly causing psychiatric symptoms in patients with AITD<sup>87,88</sup>. Also, a study of patient-reported outcomes (PROs) in Danish patients with AITD found a significant continuous reduction of outcomes, including physical functioning despite euthyroidism<sup>89</sup>. A subsequent study found reduced PROs in patients with GD compared with patients with toxic nodular goiter but failed to show an association with thyroid antibody levels<sup>90</sup>. Conversely, in studies of patients with systemic sclerosis and myasthenia gravis, those with coexistent AITD were less affected by their disease than patients without thyroid autoimmunity<sup>91,92</sup>. Thus, quantitative increments of autoimmune diagnoses are not always associated with a worsened prognosis.

The possible negative attribution of underlying autoimmunity (for example, GD) rather than thyroid function impairment (for example, multinodular goiter) needs further investigation. The presence of a more general but undiagnosed polyautoimmunity could explain the poorer outcomes of treatment. This has in recent years been acknowledged by endocrinologists and is now introduced in clinical guidelines (for example, for the treatment of hypothyroidism)<sup>93</sup>. Before combination therapy with thyroxine and triiodothyronine is considered, a search for other autoimmune diseases in a patient with AITD and poor PROs is now mandatory<sup>93</sup>. Thus, it has become relevant to both the clinician and the patient with AITD to be aware of the possibility of polyautoimmunity, not only as an explanatory model of prolonged symptoms but also with respect to a possible altered prognosis of disease and treatment outcome.

### The role of immunomodulatory biologic drugs

The prevalence of thyroid and other autoimmunity will likely be affected by the increasing administration of biologic agents in cancer treatment and internal medicine, developed to target specific parts of the immune system. In multiple sclerosis patients treated with the T cell-depleting anti-CD52 monoclonal antibody alemtuzumab, one third of patients developed GD between 6 and 31 weeks after treatment<sup>94</sup>. This was likely due to loss of T cell-mediated immunoregulation. Also, in patients with chronic hepatitis treated with interferon-alpha, up to 40% developed thyroid autoantibodies and 15% developed clinical AITD<sup>95,96</sup>. Stefan *et al.* found a direct impact of interferon-alpha on the activity of a thyroglobulin promoter region with a specific single-nucleotide polymorphism involved in AITD<sup>97</sup>. Finally, biologic drugs stimulating the patient's own immune response against cancer cells have proven efficient in fighting cancers but may induce various autoimmune diseases. Among such drugs are the checkpoint inhibitors ipilimumab (a monoclonal antibody targeting the CTLA-4 receptor) and

nivolumab and pembrolizumab (blocking “programmed cell death 1” proteins on T cells, thus promoting anti-tumor activity). Autoimmune hypophysitis is seen in 4% of patients treated with ipilimumab and in 1% of patients treated with nivolumab or pembrolizumab. Combined treatment with ipilimumab and nivolumab increases the hypophysitis rate to 8%<sup>98</sup>. In these patients with autoimmune hypophysitis, secondary adrenal insufficiency develops in up to 100%, hypogonadotropic hypogonadism in up to 85%, and central hypothyroidism in up to 100%<sup>98</sup>. More rarely, autoimmune primary thyroid affection or adrenal insufficiency occurs<sup>99</sup>. Thus, the use of such drugs should entail a standardized monitoring program to check for endocrinopathies (i.e. life-threatening adrenal insufficiency) and thorough patient information including which symptoms to react upon.

On the other hand, biologic agents may offer new options for treating (poly)autoimmune diseases, including otherwise treatment-resistant AITD. Treatment of rheumatic arthritis patients with biologic agents seems to be safe and to possibly have a positive effect on concurrent AITD<sup>100</sup>. In a small study, the treatment of 138 patients with rheumatoid arthritis with the tumor necrosis factor-alpha inhibitor adalimumab led to concurrent improvement of hypothyroidism as well as a reduction in TPOAb levels<sup>101</sup>. Incorporation of rituximab, a B cell-depleting agent, has shown promising results in patients with GO<sup>102-104</sup> in addition to ameliorating numerous other autoimmune diseases, such as rheumatoid arthritis<sup>103,105</sup>, multiple sclerosis<sup>106</sup>, and type 1 diabetes<sup>107</sup>. In a recent study, inhibition of the IGF-1R by use of teprotumumab, an antibody targeting the IGF-1R, also significantly improved outcome in 88 patients with GO<sup>108</sup>. The field of drugs targeting immune-mediated diseases is quickly evolving, and numerous drugs have been developed and are undergoing clinical trials<sup>109</sup>. Although the mechanisms triggering loss of self-tolerance are still unclear, the increasing knowledge about B-cell and T-cell subsets and different cytokine milieus provides interesting perspectives for refined treatment options in (poly)autoimmune diseases including treatment-resistant AITD. For a summary of learning points, see [Box 2](#).

### Conclusions

As illustrated above, AITD is often represented in patients with polyautoimmunity, and patients with AITD have an increased risk

#### Box 2. Learning points

- Polyautoimmunity in patients with autoimmune thyroid disease is common but not part of routine screening.
- Polyautoimmunity may increase morbidity due to inflammation.
- Patients with continuous complaints despite euthyroidism may benefit from wider immunological assessment.
- Interdisciplinary assessment is beneficial for polyautoimmune patients.
- Immunomodulatory biologic drugs may be a future treatment option in thyroid autoimmune patients with multiple associated autoantibodies.



of developing other autoimmune diseases. In AITD patients with remaining complaints despite euthyroidism or patients presenting with new symptoms, polyautoimmunity should come to mind. Furthermore, the concept of polyautoimmunity may call for a rethinking of treatment strategies in patients with AITD. Current treatment of AITD has focused on securing thyroid hormone homeostasis, but in cases with polyautoimmunity more attention should be drawn to the identification and treatment of the underlying immune dysregulation and inflammation. In years to come, immunomodulatory biologic drugs may serve this purpose.

### Author contributions

SB was in charge of the manuscript preparation. All authors contributed to the conception, discussion, critical review, and approval

of the manuscript in accordance with the requirements of the International Committee of Medical Journal Editors. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

### Competing interests

The authors declare that they have no competing interests.

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### Version 1

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