Aetiology of thyroid autoimmunity

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Abstract

Autoimmune thyroid disease (AITD) is characterised by the development of thyroid autoantibodies, mainly anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies (primarily found in Hashimoto's thyroiditis [HT]) and thyroid stimulating hormone receptor antibodies (predominate in Graves' disease [GD]). While genetic factors provide 70 to 80% of the risk for the development of thyroid autoimmunity (TAI), environmental factors contribute about 20 to 30% to the immunopathogenesis of AITD. Such environmental factors include smoking (predisposes to GD but protects against HT), alcohol (moderate consumption protects against both HT and GD), stress (predisposes to GD) and iodine (possibly increases risk of AITD). Low selenium and vitamin D levels might increase the risk of TAI, although data remains indeterminate and selenium supplementation did not always improve TAI in clinical studies. Additionally, certain drugs, toxic chemicals, infections, birth in winter and autumn and radiation exposure have also been implicated in the development of TAI. Preventive interventions to decrease the risk of AITD are limited and not always feasible, though personal and public health interventions might help with smoking and iodine exposure.

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Introduction

Autoimmune thyroid disease (AITD) is a multifactorial disorder characterised by the development of autoantibodies against particular thyroid antigens in genetically predisposed individuals, facilitated by the exposure to particular environmental factors. Anti-thyroid peroxidase antibodies (TPO-Abs), anti-thyroglobulin antibodies (Tg-Abs) and thyroid stimulating hormone receptor antibodies (TSH-R Abs), are the main autoantibodies occurring in AITD.[1] While TPO- and Tg-Abs are mainly associated with Hashimoto's thyroiditis (HT), TSH-R Abs are the main anti-thyroid antibodies found in Graves' disease (GD).[1-2] Thyroid autoimmunity (TAI) in the absence of clinical autoimmune disease is identified by the presence of these antibodies.[2]

Primary hypothyroidism caused by HT forms the bulk of clinical disease. Its incidence rises with increasing age and is more common in iodine sufficient populations.[2] The incidence rates of autoimmune hypothyroidism are 80/100,000/year in males and 350/100,000/year in females. On the other hand, the incidence rates of autoimmune hyperthyroidism are 8/100,000/year in males and 80/100,000/year in females.[3] In the third National Health and Nutrition Examination Survey, TPO-Abs were observed to be three times less prevalent in African blacks than in white Caucasians.[4]

It has been observed in twin studies that genetic factors, including polymorphisms in major histocompatibility genes (human leukocyte antigen), thyroid specific genes (e.g. TSH-R and thyroglobulin genes) and immunoregulatory genes (such as the cytotoxic T lymphocyte antigen-4 gene), provide a contribution of about 79% to the development of GD.[5-6] Similarly, genetic factors account for about 73% of the risk to develop TPO- and/or Tg-Abs.[7] Thus, environmental factors contribute about 20 to 30% to the immunopathogenesis of AITD.[6]

Existential Factors

Existential factors include age, female sex and parity.[6] In epidemiological studies, prevalence of thyroid antibodies was noted to increase with age[2,4] (although a peak of antibody positivity at around 45 to 55 years is demonstrated in a few studies).[2] GD incidence was seen to peak at an age between 20 and 49 years in two studies, between 60 and 69 years in Malmö Sweden, while it increased with age in Iceland.[8] AITD has a strong female preponderance, which may in part be explained by skewed X chromosome inactivation,[1] and in part by hormonal influences, as oestrogen appears to favour a T-helper 2 immune response, where antibody production is increased through activation of B-lymphocytes.[9]

Pregnancy is characterised by immunosuppression to protect the foetus. However, this amelioration in immunity disappears in the post-partum period, often leading to the onset/exacerbation of existing AITD.[10] In the prospective Amsterdam AITD cohort study, there were more hypothyroid cases in the postpartum period, while hyperthyroid cases were more frequent during pregnancy.[11] The reason for an association between parity and AITD might be explained by foetal microchimerism, since foetal cells have been identified in the blood and thyroid tissue of women with HT and GD. This might trigger a graft-versus-host maternal immune response, leading to autoimmune diseases.[12] However, other population-based studies contradict this hypothesis, where no association was found between previous pregnancies, parity or abortion and thyroid antibodies.[13-14]

Environmental Factors

1. Smoking

Smoking is a well-known risk factor for GD. A meta-analysis showed an odds ratio (OR) of 3.30 (95% confidence intervals [CI], 2.09, 5.22) for GD, with an even greater OR of 4.40 (95% CI, 2.88, 6.73) for Graves ophthalmopathy in current smokers when compared to never smokers. This effect is more marked in women and appears to be dose dependent. However, this risk is abolished a few years after smoking cessation, resulting in an insignificant OR of 1.41 (95% CI, 0.77, 2.58) for GD in ex-smokers compared to never smokers.[15]

On the other hand, current smoking protects against autoimmune hypothyroidism in a dose-dependent manner. This has been shown in several studies, including a population-based study by *Pederson et al,* where smoking was negatively associated with the presence of Tg-Abs more than TPO-Abs.[16] In contrast, discontinuation of smoking increased the risk for developing both TPO- and/or Tg-Abs,[17] with a 6-fold increase in overt autoimmune hypothyroidism in the first 2 years following smoking cessation, although this increased risk was transient (DanThyr study).[18]

2. Alcohol

Alcohol has been shown to protect against autoimmune hypothyroidism. In a population-based case-control study carried out in Denmark, moderate alcohol consumption (11–20 units/week) was mostly protective, irrespective of gender, smoking and type of alcohol consumed.[19] Moderate alcohol consumption (compared to abstinence/abuse) also protected against the development of GD with hyperthyroidism, thus indicating a dose-dependent relationship.[20]

3. Stress

Stress is known to be a triggering factor in the pathogenesis of GD, however, its effect on HT has been barely researched.[6] In a five-year follow-up prospective study, stress was not found to be associated with the development of TPO-Abs or with the development of hypo- or hyperthyroidism. Hypothyroid cases were in fact found to suffer from a less depressed mood than controls at the point of diagnosis, and thus the authors concluded that stress is not implicated in the development of AITD.[21]

However, in a population-based case-control study, stress and negative life events within the previous 12 months were found to be associated with the onset of GD.[22] Another case-control retrospective study confirmed a correlation between stressful life events (SLE) and the onset of GD, while no association was found between SLE and the onset of toxic nodular goitre, confirming that stress precipitates autoimmune rather than non-autoimmune hyperthyroidism.[23] Moreover, the prognosis of GD treated with antithyroid drugs appears to be worse, with higher relapse rates and TSH-R Ab titres following treatment withdrawal in individuals who suffer from mental disorders and significant stress.[24]

4. Selenium

Selenoproteins, mainly glutathione peroxidases, iodothyronine deiodinases and thioredoxin reductases are important enzymes involved with thyroid hormone metabolism, regulation of the redox state as well as protection of the thyroid gland from oxidative damage.[1] A recent large population-based study carried out in China demonstrated a higher incidence of autoimmune thyroiditis in individuals with low selenium.[25] Low selenium levels were also noted to be associated with AITD, especially GD, in another population-based study carried out in Denmark.[26]

However, the results of clinical trials testing the effect of selenium supplementation on TAI are equivocal.[1] A Cochrane database systematic review concluded that further randomized placebo-controlled trials are required to assess the effect of selenium supplementation on HT as the evidence so far is incomplete.[27]

5. Vitamin D

Although Vitamin D deficiency is associated with various autoimmune diseases including type 1 diabetes (T1D) and rheumatoid arthritis, its association with AITD is still uncertain.[1] Table 1 delineates a number of studies, where an association of AITD with vitamin D deficiency was either confirmed or refuted. Certain polymorphisms in the vitamin D receptor gene (mainly the BsmI or TaqI) were noted to confer an increased AITD risk.[28] Moreover, a recent trial has demonstrated that vitamin D supplementation causes significant TPO-Ab titre reductions.[29]

6. Infections

Several infections have been implicated in the development of AITD in genetically susceptible individuals including *Yersinia enterocolitica*, Hepatitis C virus, Coxsackie B virus, retroviruses, *Borrelia Burgdorferi* and *Helicobacter pylori* infection, particularly the cytotoxin-associated gene A strain. Infections may trigger AITD by several mechanisms, some of which may include release of sequestered antigens on cell apoptosis/destruction, molecular mimicry (an epitope on bacterium/virus is recognized as self), cryptic epitope exposure and activation of resident T-cells through inflammation and cytokine secretion.[30]

***Table 1.** Association of Vitamin D deficiency with AITD in some clinical studies.*

Study	AITD associated with Vitamin D deficiency?
Effraimidis G et al. 2012[43]	NO
D'Aurizio F et al. 2015[44]	NO
Yasmeh J et al. 2016[45]	NO
Kivity S et al. 2011[46]	YES
Bozkurt NC et al. 2013[47]	YES
Wang J et al. 2015 (A meta-analysis)[48]	YES

7. Seasonality

Hamilton et al investigated the effect of month of birth and seasonality on AITD onset in northern European Caucasian and United Kingdom populations and found no impact of month of birth on GD development. However, slightly higher birth rates in autumn were detected in HT females from the OXAGEN AITD Caucasian family collection.[31] A previous Greek study showed that male GD birth rates peaked in winter, while females with GD had two birth peaks: spring and autumn. Conversely, HT female birth rates peaked in winter, while males with HT were mostly born in winter and summer. In the general population births peaked in summer for both males and females. Therefore, they argued that both GD and HT have a similar aetiology as T1D and multiple sclerosis i.e. seasonal bacterial/viral infections during the perinatal period may be the initial trigger, as most births of AITD individuals peaked in winter and autumn.[32]

8. Drug Therapy

Several drugs may induce TAI including interferon-α, interleukin-2, campath-1H and highly active antiretroviral therapy. Instead of causing *de novo* TAI, lithium and amiodarone (an iodine rich drug) appear to be key risk factors for the development of hypothyroidism in patients with pre-existing TAI. Amiodarone's iodine load is also responsible for inducing the onset of previously subclinical GD, resulting in autoimmune thyrotoxicosis.[10]

Oestrogen use (as the oral contraceptive pill

[OCP] or hormone replacement therapy [HRT]) was found to have varied effects on TAI in different studies. It was found to be negatively correlated to TPO-Abs and was associated with a lower risk of subclinical or overt hyperthyroidism (but not autoimmune hypothyroidism) in a cross-sectional analysis of the Amsterdam AITD cohort.[33] In a Danish population-based cross-sectional study, only the use of HRT was associated with a lower occurrence of Tg-Abs (but not of TPO-Abs),[13] while no difference in thyroid antibody frequency was noted in post-menopausal women with or without HRT in a different study.[34] Furthermore, oestrogen use was found to have no correlation with thyroid antibodies in a Japanese-Brazilian population-based study.[35]

9. Radiation exposure

AITD is connected to therapeutic radiation including radioactive iodine, as well as occupational and environmental radiation exposure. Increased AITD was initially seen in atomic bomb survivors in Japan and following the radioactive fallout in Chernobyl.[36]

10. Toxic chemicals

Polyaromatic hydrocarbons including polychlorinated biphenyls (PCB) and polyhalogenated biphenyls (PBB) are organic compounds found in water and air and are made from coal. An increase in antimicrosomal and Tg-Abs together with a higher occurrence of hypothyroidism was noted in workers exposed to PBBs.[37] A higher prevalence of thyroid antibodies and an increased thyroid volume was also noted in Slovakian workers exposed to PCB.[38] Bisphenol A, perfluorinated chemicals, phthalates,[30, 36] solvents, metals, other anthropogenic compounds and petrochemical complex-related pollution have also been associated with AITD. Chemical toxins might trigger AITD by disrupting the immune system and/or interfering with thyroid function or by altering the thyroglobulin structure increasing its immunogenicity.[39]

11. Iodine

Autoimmune hypothyroidism and thyroid antibodies tend to be more prevalent in iodine replete areas and in individuals with excessive iodine intake or following iodization programmes.[1] In a Danish study, TPO and Tg-Abs became more prevalent after iodine fortification of salt, especially in young women and at low concentrations of antibody.[40] A higher prevalence of hyperthyroidism, especially in young individuals, was also noted in two areas of Denmark with moderate and mild iodine deficiency after cautious iodine fortification of salt.[41] However, a large Italian study observed an absence of an association between iodine fortification and HT or iodine induced hyperthyroidism.[42]

Table 2. *The natural history of progression of AITD.*[1]

Stage	Clinical Thyroid status	Thyroid Abs	Other changes
1	Euthyroid	Absent	Evidence of immune activation including changes in chemokines, vascular adhesion molecules, GFs cytokines and tissue remodelling factors
2	Euthyroid	Present	TSH starts getting deranged
3	Subclinical hypo/hyperthyroidism	Present	Duration longer for subclinical hypothyroidism than subclinical hyperthyroidism
4	Overt hypo/hyperthyroidism	Present	

Abs – antibodies; GFs- growth factors; TSH- thyroid stimulating hormone.

Natural history of AITD

The natural history of AITD involves four stages which are delineated in table 2. In a prospective study, progression to overt autoimmune hypothyroidism from euthyroidism took several years unlike the development of overt autoimmune hyperthyroidism which occurred after a few months.[11]

Conclusion

In conclusion, several environmental factors can affect progression to TAI. While some factors appear to predispose to both GD and HT, others may predispose to GD but protect against HT.[1] Preventive measures might involve public health interventions such as monitoring iodine intake and providing education against smoking. Promoting alcohol consumption, which has its own adverse effects, is unlikely to be feasible, while stress avoidance is not always pragmatic. Whether selenium and vitamin D supplementation can improve or protect against TAI is still indeterminate and requires further research. Other risk factors such as seasonality of birth, age and gender are non-modifiable, while avoidance of pregnancy is non-realistic.[6]

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