European Journal of Endocrinology (2004) **150** 605–618 ISSN 0804-4643

INVITED REVIEW

The environment and autoimmune thyroid diseases

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Abstract

Genetic factors play an important role in the pathogenesis of autoimmune thyroid disease (AITD) and it has been calculated that 80% of the susceptibility to develop Graves' disease is attributable to genes. The concordance rate for AITD among monozygotic twins is, however, well below 1 and environmental factors thus must play an important role. We have attempted to carry out a comprehensive review of all the environmental and hormonal risk factors thought to bring about AITD in genetically predisposed individuals. Low birth weight, iodine excess and deficiency, selenium deficiency, parity, oral contraceptive use, reproductive span, fetal microchimerism, stress, seasonal variation, allergy, smoking, radiation damage to the thyroid gland, viral and bacterial infections all play a role in the development of autoimmune thyroid disorders. The use of certain drugs (lithium, interferon-α, Campath-1H) also increases the risk of the development of autoimmunity against the thyroid gland. Further research is warranted into the importance of fetal microchimerism and of viral infections capable of mounting an endogenous interferon-α response.

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Introduction

Graves' hyperthyroidism, Hashimoto's hypothyroidism and post-partum thyroid dysfunction are common disorders. They have an autoimmune origin and are therefore also alluded to as autoimmune thyroid disease (AITD). Like other organ-specific autoimmune endocrinopathies, e.g. type I diabetes mellitus (IDDM), they have a multifactorial etiology. Genes are certainly involved and in order to develop AITD a subject will have a certain genetic susceptibility, probably involving multiple genes of which only a few have been identified. Most notably, certain human leukocyte antigen (HLA)-DR genes determine this genetic susceptibility, but there are other genes involved and AITD thus has a polygenetic background. Nevertheless, non-genetic (environmental, hormonal) factors must also play an important etiologic role, because the concordance rate for AITD in monozygotic twins is not 100%. Another argument is that immigrants coming from countries with a low incidence of autoimmune diseases will adopt the incidence rate of the new country. For instance, type I diabetes mellitus is 10 times more frequent in Pakistanis living in the UK than in those living in Pakistan (1).

In recent years, a number of excellent reviews have been published on the genetic background of AITD (2–6). Here we will attempt to review the environmental factors that may be involved in the development of AITD (Table 1). In this review we will consider both Graves' disease and Hashimoto's thyroiditis. Despite their different phenotype, they do share some homology. First, autoantibodies against thyroid peroxidase (TPO) are common in both diseases. Secondly, Graves' disease and Hashimoto's thyroiditis appear to run in the same families and thus share a common genetic background (7, 8).

Fetal growth

Reduced fetal growth is a risk factor for several common disorders, such as chronic heart disease (9), and famine exposure during fetal life is associated with subsequent glucose intolerance during adult life (10). Prenatal malnutrition is associated with a lower thymic and splenic weight (11), and this may cause earlier maturation of the thymus resulting in a decline in T suppressor cells (12). Indeed, Phillips *et al.* (12) found that among 305 women aged 60–71 years born in the UK the presence of TPO antibodies was positively related to lower birth weights (but not to weight at 1 year of age). The prevalence of TPO antibodies was 2.4 times higher in women with a birth weight of less than 5.5 lbs (2.49 kg) compared with those with a higher birth weight. In a twin study, the same group found that among monozygous twins, the smaller twin had higher levels of TPO antibodies (13). Because of the genetic identity of monozygous twins, this study strongly suggests

Table 1 Environmental factors involved in the etiology of AITD.

Environmental factor	Mechanism	Phenotype
Low birth weight	Insufficient thymic maturation	TPO antibodies
Iodine excess	No escape from Wolff–Chaikoff effect	HT
	Jod-Basedow	GD
Selenium deficiency	Unknown; viral infections?	HT
Longer reproductive span	Estradiol effect?	HT
Oral contraceptives	Protective	TPO antibodies
Fetal michrochimerism	Male cells in thyroid elicit antithyroid attack	HT and GD
Stress	Upregulation HPA axis	GD
Allergy	Unknown; high IgE levels	GD
Smoking	Hypoxia? High IgE levels	GD; esp. GO
Yersinia enterocolitica infection	Molecular mimicry	GD

See text for explanation and references. GD, Graves' disease; HT, Hashimoto's thyroiditis; GO, Graves' ophthalmopathy.

that certain intrauterine factors causing reduced fetal growth are the first environmental risk factors for AITD in later life. However, this was not confirmed in another twin study where birth weight was not found to be a determinant for clinically overt AITD (14).

Iodine intake

Iodine intake seems to influence the prevalence rates of hyper- and hypothyroidism. In areas with sufficient iodine intake, hypothyroidism is more common than in iodine-deficient regions (15), whereas the overall prevalence of thyrotoxicosis is greater in iodine-deficient areas (16). Looking at the different causes of hyperthyroidism, Graves' hyperthyroidism as the cause of thyrotoxicosis is seen more frequently in iodine-replete areas (17), and TPO antibodies as a marker for impending thyroid failure are more prevalent in iodine-deficient regions (18).

Excessive iodine intake can cause dysthyroidism, especially in patients with underlying autoimmune thyroiditis (19). Due to a failure to escape from the Wolff–Chaikoff effect, iodine excess can cause hypothyroidism and/or goiter, but if autonomously functioning nodules or a subclinical form of Graves' disease are present, it can also induce hyperthyroidism (Jod–Basedow effect) (20, 21). Both phenomena are thought to lead to some thyroid destruction and hence presentation of thyroidal antigens to the immune system leading to an autoimmune reaction (22). It thus appears that iodine intake is indeed a risk factor for the development of AITD. This is in agreement with animal studies showing that a high iodine intake aggravates autoimmune thyroiditis in several genetically susceptible animal strains (23–25).

Selenium intake

Selenium is a trace mineral and an essential nutrient for selenocysteine synthesis and is also called the 21st amino acid. It is incorporated into 35 selenoproteins, mostly enzymes (26). Selenium also has a marked influence on the immune system and selenium deficiency is associated with a greater susceptibility for viral infections such as the Coxsackie virus (27), possibly because T-lymphocytes have an important functional need for selenium (26). In addition, selenium acts as an antioxidant and reduces free radical formation. It plays an essential role in thyroid hormone synthesis, because two enzymes involved in thyroid hormone production are selenoproteins: the deiodinases and glutathione peroxidase (28). Selenium deficiency leads to a variety of symptoms including a higher miscarriage rate (29) and a higher cancer mortality rate (26).

Selenium intake in Europe is lower than in the United States and in many countries it is below the UK reference nutrient intake of 75 μg/day. Sources of selenium are crab, other shellfish and fish, but alternative sources such as wheat are relatively low in selenium content because of the low selenium availability in European soils (26).

Low selenium blood levels are associated with increased thyroid volume and with thyroid hypoechogenicity, a marker for lymphocytic infiltration (30). In agreement with this finding, a recent double-blind randomized trial in patients with subclinical hypothryoidism showed that treatment with 200 μg sodium selenite caused a significant decrease in TPO antibody titers (as well as an increase in quality of life), without affecting thyroid hormone status (31). In another randomized trial in patients with subclinical hypothyroidism who were treated with thyroxine supplementation, addition of 200 μg selenium methionine led to a significant decrease in TPO antibody concentrations (32).

Hormonal influences: female sex

One of the most striking characteristics of organ-specific autoimmune diseases is its female preponderance. The female:male ratio for Graves' disease and

Hashimoto's thyroiditis is 5–10:1 (33). The reason for this is unclear and genetic factors must play a role, although it is noteworthy that Hashimoto's thyroiditis is very prevalent among girls with Turner's syndrome (XO karyotype), but not in men with Klinefelter's syndrome (XXY karyotype) (6). The influence of the X chromosome is thus limited and *hormonal* influences may also be operative in the induction of AITD. It is interesting to note the female preponderance in non-autoimmune-mediated thyroid disease, such as multinodular goiter, but this is outside the scope of this review.

Parity

Silent thyroiditis frequently occurs in the post-partum period, hence the name post-partum thyroid dysfunction, but Graves' disease is also often seen in the first months post-partum. During pregnancy, the immune system is suppressed with a fall in the T-helper/suppressor-cell ratio, whereas in the first post-partum months T-cell activation occurs and thyroid autoantibody production rises (34). The immune suppression during pregnancy suggests that high levels of estradiol (E_2) may prevent autoimmunity, which is indeed true in several animal models for T-helper (Th)-mediated diseases (35). This immune suppression is associated with a decrease in the severity of Th1-mediated autoimmune diseases such as type I diabetes mellitus, rheumatoid arthritis and multiple sclerosis, whereas systemic lupus erythematosus (SLE) often worsens or remains unchanged during pregnancy (36). This has been attributed to a shift in the Th1/Th2 balance towards Th2 immunity to protect the fetus. This paradigm has recently been challenged and does not explain why Graves' disease, as a clearly autoantibody-mediated disease, also abates during pregnancy.

On the other hand, the hyperprolactinemia of the post-partum period suggests that prolactin may act as an immunostimulant, although prolactin levels are also clearly elevated during pregnancy. In a large survey among 1877 subjects, hyperprolactinemia was found not to be associated with AITD (37).

It is possible, therefore, that parity itself is responsible for the gender difference in AITD, but no relation could be found between Hashimoto's thyroiditis and parity (38). In this study, however, a lower risk for Hashimoto's thyroiditis was found in subjects with a later age at menarche ($\geq$15 years) and a higher risk with a later age at menopause ($\geq$51 years), resulting in a higher risk for Hashimoto's thyroiditis in women with longer reproductive spans.

Oral contraceptives

Another link to explain the sex difference would be the use of oral contraceptives or hormone replacement therapy (HRT). The latter, however, was found not to be associated with either subclinical hypothyroidism or the presence of TPO antibodies (39), although in one case report an exacerbation of eye symptoms was seen in a woman with Graves' ophthalmopathy starting HRT (40). As for oral contraceptives, used by over 100 million women worldwide (41), there are remarkably few studies on their use and the development of AITD and in contrast to what one intuitively may think their use seems to protect against AITD. In an early large study among 46 000 women, cases of hypo- or hyperthyroidism together were seen less frequently among oral contraceptive users than in controls (relative risk (RR), 0.68; 95% confidence interval (CI), 0.52–0.85) (42). Two large population-based studies found that thyroid volume was smaller in oral contraceptive users than in controls (43, 44). We found that estrogen use protected against the development of hyperthyroidism, independently of the number of previous pregnancies (7). This is in agreement with the observation that the use of contraceptives had a protective effect for the development of Graves' disease (odds ratio (OR), 0.68; 95% CI, 0.49–0.93), but not for Hashimoto's thyroiditis (45).

Fetal microchimerism

Lastly, a new concept has emerged that may explain the female preponderance: fetal microchimerism. This involves the transfer of fetal cells into the maternal circulation. These fetal cells can persist for a long time (46), and the consequences of the presence of semi-allogeneic cells for autoimmunity are currently being explored, also in the field of AITD (47). Imaizumi *et al.* (48) found fetal cells in the thyroid glands of 12/46 (46%) of Tg-immunized pregnant mice as compared with only a small number in 2/10 (20%) of control pregnant mice. The same group then found that fetal cells were more often present in thyroid glands of patients affected by Graves' disease than in nodular thyroids (49). Klintschar *et al.* (50) found intrathyroidal fetal cells in 8/17 (47%) Hashimoto patients compared with only 1/25 controls.

This is an exciting new discovery, and it may be that these engrafted semi-allogeneic cells trigger autoimmunity towards the organ in which they live and it has now been implicated in several other autoimmune diseases including systemic sclerosis and Sjögren's syndrome (47, 51).

Stress

Stress has a profound influence on the immune system through neuroendocrine networks (52, 53). During stress the hypothalamo–pituitary–adrenal (HPA) axis becomes activated, which would imply that stress has an immunosuppressive effect. However, it is becoming clear that stress and corticosteroids have a differential

effect on Th1 and Th2 cells, driving the immune system towards a Th2 response. It thus suppresses cellular immunity and facilitates the persistent presence of certain viruses (such as Coxsackie B), while humoral immunity is enhanced. This may explain why certain autoimmune diseases are often preceded by severe stress (54, 55), and Graves' disease seems to be one of them.

The possible relation between stress and Graves' hyperthyroidism was noted in the early descriptions by Parry, Graves and von Basedow. Later it was noted that there was always a major increase in the occurrence of Graves' disease during wartime, a condition called 'Kriegsbasedow' (56). For example, the incidence of Graves' disease in Denmark became 4-fold higher in 1942 as compared with 1940 (57). A good recent example for this is the increase in Graves' disease during the civil war in Yugoslavia (58). However, there are exceptions because no increased frequency of Graves' disease was found in Belfast during the civil unrest there (59). Apart from war, the association has also been studied in a number of formal case–control studies. The first study from Sweden established an association between negative life events in the year preceding the diagnosis of Graves' hyperthyroidism (60). This was later confirmed by various other studies (61–63). However, these case–control studies can and have been criticized because of their retrospective nature, the influence of recall bias and the fact that hyperthyroidism itself is associated with increased anxiety (64, 65). Nevertheless, treatment with a benzodiazepine reduced the relapse rate in a retrospective study from 74% in untreated patients to 29% in treated patients (66). In a recent prospective study, it was shown that four personality traits (hypochondria, depression, paranoia and mental fatigue) were positively related to the relapse rate after antithyroid drugs in Graves' disease, and that stressful life events correlated with the titer of thyroid-stimulating hormone (TSH)-receptor antibodies (67). Another case–control study found that Graves' disease patients had had a significantly greater number of stressful life events than patients with toxic nodular goiter or controls (the latter two groups were not different from each other in terms of stressful life events) (68).

Whether stress is also related to Hashimoto's disease is unknown, but we could not find a relationship between stressful life events and daily hassles with the presence of TPO antibodies in euthyroid subjects (T Strieder, unpublished observations).

Seasonal variation

The incidence of myxedema coma is higher in the winter (provoked by lower ambient temperatures), whereas thyrotoxicosis is more often diagnosed in the warmer periods of the year (69, 70). The seasonality of thyrotoxicosis may not be related to the warmer temperatures (71), but to the fact that milk (in the UK the major source of iodine) contains more iodine in winter than in summer (72). Another factor responsible for seasonal differences may be the seasonal variation in viral infections or in allergen exposure.

Allergy

Allergic diseases (being Th2 disorders) and autoimmune diseases (Th1 mediated) are usually considered as the opposites in immune reactions, but this contention is now less evident because allergy-associated mechanisms can contribute to the pathogenesis of autoimmune diseases such as multiple sclerosis (73). A recent study showed that there is an association between the presence of wheezing as a measure of asthma and the occurrence of type I diabetes (74). Similarly, an association was found between an allergic constitution (asthma, atopic eczema) and AITD with OR values of 2.54 (95% CI, 1.16–5.57) and 2.95 (95% CI, 1.37–6.34) (75). Furthermore, there is a correlation between elevated levels of immunoglobulin E (IgE) and a slower decrease in TSH-receptor autoantibody levels in patients with Graves' disease (76). Patients with elevated IgE levels also have a lower chance of remission of Graves' disease after antithyroid drug treatment: remission levels of 20/41 (49%) versus 53/66 (80%; $P = 0.0014$) were reported in patients with elevated and normal levels of IgE respectively (77). In addition, patients with a relapse of Graves' hyperthyroidism had a higher rate of allergic rhinitis attacks (34%) than those who went into remission (7%) (78). The same authors reported on a TPO-antibody-positive patient who developed Graves' disease shortly after a severe allergic rhinitis due to an allergy to Japanese cedar pollen, with a concomitant rise in IgE levels, and suggested that allergic rhinitis is another risk factor for Graves' disease (79).

There is also an association between another allergic disease, chronic urticaria, and Hashimoto's thyroiditis (80). TPO and/or Tg autoantibodies were found more frequently in patients with chronic urticaria and angioedema (11.7%) than in controls (3.7%) (81), confirming an earlier report that found that 14% of urticaria patients had evidence for thyroid autoimmunity, more than statistically expected (82).

Smoking

Apart from being a risk factor for cardiovascular diseases and lung carcinoma, cigarette smoking also has an influence on the immune system. Smoking induces a polyclonal activation of both B and T cells enhancing interleukin (IL)-2 production (83); it can also stimulate the HPA axis (84). Smoking (including passive smoking) increases serum IgE levels (85) and increases

the risk of allergic symptoms (86). Smoking may also increase the presentation of antigens by damaging cells and this mechanism has been proposed in the pathogenesis of Goodpasture's syndrome (83). It may also explain why anti-heat shock protein (hsp)72 antibodies are more frequently found in smokers than in non-smokers (87). Smoking also appears to induce the production of several cytokines such as soluble IL (sIL)-2-receptor (88), sIL-1-receptor antagonist (89), soluable Intracellular Adhesion Molecule (sICAM)-1 (90), and IL-4 but not interferon-γ (IFN-γ) (91).

Smoking is linked to autoimmune diseases and increases the risk for rheumatoid arthritis, with an RR of 3.8 (92). It is also associated with Graves' hyperthyroidism with an RR of 2.62 (95% CI, 2.01–3.38) (93), but it is especially related to Graves' ophthalmopathy as was first reported by Hägg & Asplund (94). In our own study (95), we found an RR for ophthalmopathy of 7.7 (95% CI, 4.3–13.7), and the RR increased significantly from 2.5 for mild eye disease to 27.2 for severe eye disease (95). Similar results were obtained by others, with an RR for ophthalmopathy of 4.66 (95% CI, 3.46–6.27) in Italy (96) and 8.15 (95% CI, 2.81–23.64) in Taiwan (97). In most studies a dose–response relationship between smoking and disease severity was found (98–101). In a recent meta-analysis, the overall OR associated with smoking was 4.40 (95% CI, 2.88–6.73) (93).

If smoking increases the risk for Graves' ophthalmopathy via immunological mechanisms, one would expect it to be also related to autoimmune hypothyroidism. Although one study found an RR of 3.9 (95% CI, 1.6–9.1) (102), a meta-analysis could not confirm this: OR, 1.71 (95% CI, 0.87–3.39) (93). On the other hand, smoking was found to be a risk factor for the development of post-partum thyroid dysfunction: OR, 1.97 (95% CI, 1.23–3.17) (93). We recently found that smoking is negatively associated with the presence of TPO antibodies in euthyroid females and thus seems to protect against autoimmune thyroiditis (7).

The association between smoking and Graves' disease is further underscored by the fact that smoking increases the risk for a relapse of Graves' hyperthyroidism (103, 104). Smoking also increases the chances of an exacerbation of the eye disease after treatment with ^{131}I, and it reduces the efficacy of radiotherapy and corticosteroid treatment of the ophthalmopathy (105, 106).

The reason for the strong association of smoking with Graves' ophthalmopathy is largely unknown (107). Hypoxia may play a role (108), because fibroblasts show a significant increase in proliferation and glycosaminoglycan production when cultured under hypoxic circumstances (109). Nicotine itself may also be involved, since nicotine addition to cultured orbital fibroblasts increased the expression of HLA-DR (110).

Drugs

Several drugs are known to induce AITD in genetically predisposed individuals, but the mechanisms by which they have this effect are different (Table 2).

Amiodarone

Thyroid dysfunction is a frequent side-effect of amiodarone, occurring in approximately 15% of patients (111). Neither amiodarone-induced hypothyroidism nor thyrotoxicosis are autoimmune mediated, although both do occur more frequently in females with thyroid antibodies (112). Whether amiodarone can induce autoimmunity is uncertain (111, 113). An early report that amiodarone induced a transient presence of TPO antibodies (114), could not be confirmed by others (115, 116).

Antiretroviral therapy

Highly active antiretroviral therapy (HAART) has been found to be associated with Graves' disease, occurring 16–19 months after initiation of different combinations of indinavir, stavudine, lamivudine and ritonavir (117). It may be related to HAART-induced changes in CD4 T cells (118).

Campath-1H

This humanized anti-CD52 monoclonal antibody induced Graves' disease in one-third of patients with multiple sclerosis treated with this compound (119). The reason for this is unknown, but since multiple sclerosis is not associated with AITD and the patients in whom Graves' disease occurred were not predisposed to the development of AITD (they lacked TPO antibodies), the effect should be related to the antibody. Campath-1H suppresses Th1 lymphocytes and thus shifts the Th1/Th2 balance towards antibody production and hence apparently towards a humoral immune response against the TSH-receptor (22).

Table 2 Drugs associated with the induction of AITD.

Drug	Mechanism	Phenotype
Amiodarone	Thyroid damage, iodine excess	Uncertain: HT
HAART	Changes in CD4+ cells	GD
Campath-1H	Decrease in Th1/Th2 ratio	GD
IFN-α	Stimulation of ADCC	HT
	Stimulation of Th1 cells	GD
IL-2	Activation of T cells	HT

For explanations and references see text. HAART, highly active antiretroviral therapy; IFN, interferon; IL, interleukin; ADCC, antibody-dependent cellular cytotoxicity; HT, Hashimoto's thyroiditis; GD, Graves' disease.

IFN-α

IFN-α is widely used in the treatment of hepatitis C virus infection (120). Unlike IFN-γ (121), it is strongly associated with the induction of AITD (122). Risk factors for the development of autoimmune thyroid dysfunction include the female sex (RR, 4.4; 95% CI, 3.2–5.9) and the pretreatment presence of TPO antibodies (RR, 3.9; 95% CI, 1.9–8.1) (122). IFN-α treatment can induce three types of thyroid dysfunction: autoimmune hypothyroidism, destructive thyroiditis and hyperthyroidism. These can occur at any time after the start of treatment with a median of 17 weeks (123). Hypothyroidism is slightly more frequent than thyrotoxicosis, and in the large majority of cases it is of autoimmune origin leading to permanent thyroid failure in approximately 60% of patients (124, 125). Graves' hyperthyroidism is the cause of thyrotoxicosis in about half of the patients; the rest suffer from silent thyroiditis.

IFN-α is a type I interferon (like IFN-β, but not IFN-γ which is a type II IFN) and stimulates Th1 development (126). It has strong antiviral activity by promoting HLA-I class I expression leading to recognition of virus-infected cells by cytotoxic T-lymphocytes (127). It also enhances antibody-dependent cell-mediated immunity by upregulating Fc-receptor density on lymphoid cells (128). Since infections with various viruses stimulate endogenous IFN-α production (129), we postulated that viral infections may also precipitate AITD via this IFN pathway (see below) (122).

IL-2

IL-2 is used in the treatment of HIV infection and in metastatic renal carcinoma and melanoma. Its pleiotropic immune effects include activation of T cells and among them autoreactive lymphocytes (130). IL-2 is involved in autoimmunity and it was shown recently that labeled IL-2 could be used to visualize sites of autoimmune inflammation in the pancreas of pre-diabetics and in Hashimoto's thyroiditis patients (131). Short-term IL-2 administration induces an increase in serum thyroxine (T_4), 3,5,3′-triiodothyronine (T_3) and TSH levels, probably via a direct central stimulation of the pituitary (132); long-term use is associated with hypothyroidism, occurring in as many as 16% of patients (130). However, in most of these patients other therapies (lymphokine-activated killer (LAK) cell infusion) were used concomitantly and the hypothyroidism was not always of autoimmune origin (133, 134).

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

GM-CSF may activate mature lymphocytes and hence aggravate or induce autoimmunity against the thyroid (130). Nevertheless, such a side-effect has been reported only rarely (135). In one study among 25 patients, only two patients with pre-existing TPO antibodies suffered from transient hypothyroidism (136). In another study, however, no thyroid dysfunction was found among 20 patients treated with GM-CSF despite the fact that two had positive antithyroidal antibodies (137).

Irradiation

Irradiation of the thyroid gland may expose thyroidal antigens to the immune system and thus induce autoimmunity by stimulation of dendritic cells (138). Both external irradiation and internal irradiation by ^{131}I are associated with AITD.

External irradiation

External irradiation is a clear risk factor for the induction of thyroid cancer, but also of hypothyroidism. In a large series of 1677 patients irradiated to the neck because of Hodgkin's disease, hypothyroidism was found in 47% after a median of 4.0 (0.2–23.7) years after treatment (139). This is probably caused by damage to the gland and is not autoimmune mediated. However, external irradiation is also associated with Graves' disease, occurring in 3.3% of the patients in the same study. This was confirmed in another study, where Graves' disease was diagnosed in 5% of 1791 irradiated patients; an 8-fold greater incidence rate than in controls (140). The reason for this association may lie in the exposure of TSH-receptor protein to the immune system and this may also be the reason that external neck irradiation also enhances the risk for Graves' ophthalmopathy (141–144).

^{131}I therapy

Radioactive iodine is frequently used in the treatment of Graves' hyperthyroidism and multinodular goiter. In the last decade, it has become clear that it can induce the occurrence of Graves' hyperthyroidism in patients treated for (non-)toxic multinodular goiter (145, 146). This complication typically occurs after 3–6 months and is seen in 4–5% of cases; it occurs in parallel to an increase in TSH-receptor autoantibodies (147, 148). Interestingly, TSH-receptor antibodies were not induced in ten patients without this complication, indicating that this induction only occurs in otherwise – genetically – predisposed individuals (147).

Environmental radiation (nuclear fall-out)

In addition, environmental radiation exposure such as occurred after the dropping of the nuclear bombs on

Nagasaki and Hiroshima, or the Chernobyl nuclear plant accident, may also damage the thyroid and expose antigen to the immune system. Indeed, the survivors of the atomic bomb on Nagasaki not only have an increased risk of thyroid cancer, but also of antibody-positive hypothyroidism (149). The same appears to be true for the people exposed to the Chernobyl fallout. In one case–control study, the OR for the development of TPO antibodies was 6.89 (95% CI, 3.17–14.99) and was higher in girls (9.64) than in boys (4.19) (150). This was confirmed in another case–control study, where 18.9% of children in the exposed area had TPO antibodies versus only 5% of controls from a non-exposed region in southwestern Russia (151). There was no difference in thyroid volume or function. However, there are also a number of studies that failed to find an association with TPO antibodies (152–155). Nevertheless, when Eheman *et al.* (156) reviewed the literature they concluded that low-dose environmental radiation exposure may be associated with the development of AITD.

Viral infections

In view of the association between IFN-α and AITD, it has been suggested that viruses causing high endogenous IFN-α levels may also be associated with the induction of AITD. One such virus is the Coxsackie B virus, which has been implicated in the induction of type I or insulin-dependent diabetes mellitus (IDDM). Evidence of a recent Coxsackie B infection was found more frequently in children who developed IDDM than in controls (157–159). In another study, 39/56 (70%) patients with IDDM of recent onset had high IFN-α levels and in half of them the Coxsackie B virus could be detected, while the virus was absent in IDDM patients with low IFN-α levels (160). In line with this, IFN-α induction by injection of polyinosinic polycytidylic acid (Poly IC) could induce IDDM in a rat strain that does not spontaneously develop IDDM (161).

IFN-α may thus act as a non-specific stimulus of the induction of autoimmunity. However, whether AITD is associated with viral infections is unknown since no studies like those mentioned above have been done in this field. Only congenital rubella infection, a strong risk factor for IDDM (162), is known to be associated with the presence of TPO antibodies in children, but this syndrome is very rare (163). In addition, there have been reports on the presence of retroviral sequences and proteins in thyroid glands from patients with AITD such as the gag protein from the human foamy virus (HFV) (164). The importance of this virus is doubtful, because HFV sequences can be found in blood lymphocytes from both Graves' disease patients and healthy controls (165). Viruses are thought to induce De Quervain's thyroiditis; however, this is not an autoimmune condition but rather an inflammatory disorder with high levels of C-reactive protein (166).

Bacterial infections

Several autoimmune diseases have been linked to bacterial infections, including Graves' disease (Table 3) (167). There are several hypotheses to explain this association. The first implies molecular mimicry (168). Bacterial pathogens can have an antigen sharing homology with a self-antigen and an immune reaction against the bacterial antigen may then lead to a breakdown of self-tolerance resulting in autoimmunity. This mimicry is not restricted to similarity in amino acid sequences. An autoreactive T cell line derived from a patient with multiple sclerosis, recognizing myelin basic protein (the autoantigen in multiple sclerosis) presented by a certain HLA-DR 2b protein, also recognized an Epstein–Barr virus peptide (with no homology to myelin basic protein) presented by a different HLA-DR 2a molecule (169). Here, it was not the two antigens but the two antigen–HLA complexes that shared the homology (170).

The hsps present on bacteria, but also expressed by human cells in response to inflammation and other stresses (171), provide another link between bacterial infections and autoimmunity (172). T-cell reactivity against hsp60 present on *Salmonella typhimurium* is thought to cause reactive arthritis because of cross-reactivity (173). A link with thyroid autoimmunity may be suggested by the observation that Graves' disease patients have higher levels of anti-hsp72 antibodies than controls (87, 174).

Table 3 Some examples of autoimmune disease linked to bacterial infections via molecular mimicry; adapted from Ebringer & Wilson (167).

Disease	Autoantigen	Bacterial pathogen
Rheumatic fever	Cardiac myosin	*Streptococcus pyogenes*
Ankylosing spondylitis	HLA-B27	*Klebsiella pneumoniae*
Rheumatoid arthritis	Type XI collagen	*Proteus mirabilis*
Rheumatoid arthritis	hsp60	*Mycobacterium tuberculosis*
Graves' disease	TSH-receptor	*Yersinia enterocolitica*

Another explanation linking autoimmunity to bacterial infections is the release of sequestered antigens by local infection and inflammation (175). In this respect it seems worth noting that TSH-receptor protein is expressed by intestinal lymphocytes (176, 177).

Whether bacterial infections play a role in AITD has not been studied, with one noticeable exception: *Yersinia enterocolitica.*

Y. enterocolitica *infection*

This is an intestinal Gram-negative pathogen from the same family as the notorious *Y. pestis* (178). It mostly causes a self-limiting enterocolitis, but may persist as a low-grade infection of the mesenteric lymph nodes characterized by the persistence of antibodies against *Yersinia* outer membrane proteins (YOPs) (179, 180). This may be common, because in one case–control study approximately 25% of both cases (with chronic fatigue syndrome) and controls had IgG anti-YOP antibodies (179).

In the 1970s two studies reported a higher prevalence of *Y. enterocolitica* (especially serotype O:3) antibodies in Graves' disease patients (50 and 66% respectively) than in controls (28 and 8% respectively) (181, 182). These findings prompted an investigation into the possibility of shared antigens with the thyroid and it was found that *Y. enterocolitica* had specific binding sites for TSH in the 10^{-8} M range (183). These binding sites were also recognized by TSH-receptor autoantibodies (184). Antibodies against YOPs raised in rabbits displaced TSH from binding to TSH-receptor protein, and these antibodies stained thyroid epithelial cells in immunohistochemistry (185, 186). Cellular immunity is also involved, because *Y. enterocolitica* can inhibit the migration of lymphocytes from patients with Graves' disease (181), and in a mouse model *Y. enterocolitica* acts as a superantigen (187).

The cross-reacting protein(s), at first thought to be the TSH-receptor itself, has not been identified yet, but appears to have conformational homology with the TSH-receptor, and one may be hsp70 (188). Others have found two low molecular weight envelope proteins (of 5.5 and 8 kDa) that are cross-reactive with the extracellular part of the TSH-receptor (189). The protein(s) do not seem to be *Y. enterocolitica* specific, since TSH binding sites were also found on other intestinal pathogens (190).

Y. enterocolitica infections are common. In a large Danish study, 8.3% of 48 857 patients with bacterial enteritis had a *Y. enterocolitica* infection (191). In Canada, the annual incidence of *Y. enterocolitica* infections is 3/100 000 subjects (192); in The Netherlands the yearly incidence is 1.2/100 000 inhabitants (193). In view of the high incidence of AITD, *Y. enterocolitica* infections may thus play a role in its development. With more specific assays using YOPs, there is indeed an association between antibodies against YOPs and AITD. IgA antibodies are thought to indicate that the primary immune response is mounted in the gut, and not in the thyroid, suggesting the *Y. enterocolitica* infection is causative (194). In a German study, IgG class antibodies were found in 72% of Graves' patients and in 66% of patients with Hashimoto's thyroiditis as compared with 35% in controls; IgA antibodies were found in respectively 33, 37 and 11% (195). In Greece, 25% of Hashimoto patients had IgG antibodies and 2.8% had IgA antibodies, compared with 2 and 0% respectively in controls (196). A higher incidence of *Y. enterocolitica* antibodies in Graves and Hashimoto patients than in controls was also found in Japan and Turkey (197, 198). However, there are also studies that could not confirm these findings and found a similar rate of seropositivity in AITD patients and controls (199, 200). We recently found that 40% of 803 female relatives of patients with documented AITD had IgG antibodies against *Y. enterocolitica* YOPs (22% had IgA antibodies), as compared with only 24% of controls (13% had IgA antibodies), but the presence of these antibodies was unrelated to the presence of thyroid autoimmunity (201). We hypothesized that this high rate of probably persisting, low-grade *Y. enterocolitica* infections in relatives of AITD patients is related to a particular genetic make-up facilitating *Y. enterocolitica* infections independently from conferring a risk for AITD.

Concluding remarks

AITD is a polygenetic disease and currently only a few genes have been identified as causing AITD, all with a rather low RR which is seldom higher than 3.0. Nevertheless, it has been calculated that 79% of the susceptibility to develop Graves' disease can be attributed to genetic factors, leaving 21% for environmental factors (202). Reviewing these non-genetic factors, it appears that multiple environmental factors are involved in the induction of AITD in genetically predisposed individuals (Table 4). It follows that there must be an interplay at work between different genes and different environmental factors. For instance, the post-partum period is a clear risk factor for Graves' disease but cannot explain its occurrence in males and only a minority of women will develop Graves' disease in the post partum period. In other words, one gene may predispose for AITD in general while a second gene may dictate whether childbirth will precipitate its onset or not, while in another woman with the same first susceptibility gene the trigger may lie in a stress-coping gene. This would explain the rather low OR values of individual – genetic and environmental – risk factors: a specific environmental risk factor may have a very large RR in a person with a certain genetic make-up.

This implies that the true importance of both genes and environment can only be discerned when studied

Table 4 Odds ratio (OR) and 95% confidence intervals (95% CI) of several environmental factors associated with the occurrence of AITD.

Environmental factor (phenotype)	**OR**	**95% CI**	**Cases/controls**	**Reference**
Low birth weight (< 5.5 lb; Tg antibodies)	5.5	1.0–30.1	113/190	Phillips *et al.* (12)
High selenium levels (hypoechogenicity)	0.2	0.06–0.7	Logistic regression	Derumeaux *et al.* (30)
High age at menopause (> 50 years; HT)	3.0	2.0–6.0	47/47	Phillips *et al.* (38)
Use of oral contraceptives (GD)	0.68	0.49–0.93	617/617	Vestergaard *et al.* (45)
Fetal microchimerism				
(HT)	21.3	2.3–195	17/25	Klintschar *et al.* (50)
(GD)	5.3	0.58–48	27/10	Ando *et al.* (49)
Stress (GD)	3.37	2.4–4.7	387/524	Winsa *et al.* (60) Sonino *et al.* (61) Kung (62)
Smoking				
(GD)	3.3	2.1–5.2	949/5781	Vestergaard (93)
(GO)	4.4	2.9–6.7	768/1775	
Allergy (relapse rate GD)	4.3	1.8–10.1	44/73	Komiya *et al.* (77)
*Y. enterocolitica** (GD)	4.3	3.2–5.9	245/749	Bech *et al.* (181) Shenkman & Bottone (182) Wenzel *et al.* (195) Corapcioglu *et al.* (198) Arscott *et al.* (199)

* Studies reporting positive IgA antibodies, or antibodies against serogroup O:3. GD, Graves' disease; GO, Graves' opthalmopathy; HT, Hashimoto's thyroiditis.

in conjunction. Such an approach requires a much larger sample size and probably multi-center cooperation. The good news is, however, that we now have powerful computers to perform the necessary multivariate analyses. It also means that we need a much more rigorous phenotype definition. Environmental risk factors are more likely to be important in older patients with AITD than in younger ones, their influence may also differ between patients who come from a family of AITD patients and isolated cases, or between males and females.

This does not mean that a further search for specific risk factors is useless. When reviewing all factors, one of the most promising is fetal microchimerism. To date this has been limited to the search for remnants of male fetuses (the Y chromosome), but female fetuses are likely to have the same impact. This implies further studies into the genetic make-up of partners of AITD patients. A second area holding promise is the importance of viral infections in the induction of AITD. They appear to be of importance in the induction of IDDM, lead to an endogenous surge in IFN-α (a clear risk factor for AITD when administered as a drug) and are more likely to occur in selenium deficiency (which is itself another risk factor for AITD).

The ultimate goal of this research is to find a feasible way of preventing the occurrence of AITD; for this we will need progress both in delineating the genetic background and in clarifying the precipitating environmental factors.

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Received 15 December 2003
Accepted 10 February 2004