Environmental factors and thyroid autoimmunity

Facteurs environnementaux et auto-immunité thyroïdienne

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Abstract

Thyroid autoimmune disease, a multifactorial organ-specific autoimmune disorder, is marking a constant increase worldwide. It is thought to be caused by multiple environmental factors triggering autoimmune response in genetically susceptible individuals, though the exact mechanisms linking environmental factors to thyroid autoimmunity are not as yet well understood. Nevertheless, there is increasing evidence that mainly nutritive factors and environmental pollution by metals and chemicals (e.g. organochlorines, pesticides) are the main factors in the present-day spread of this disease. This review presents an overview of the current knowledge regarding environmental factors, their association with genetics and their impact on the immune system.

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Keywords: Iodine; Selenium; Nutrition; Pollution; Thyroid autoimmunity

Résumé

L’auto-immunité antithyroïdienne constitue un désordre spécifique d’organe d’origine multifactorielle, qui partout dans le monde se révèle en constante augmentation. On pense qu’elle est provoquée par des facteurs environnementaux multiples qui déclenchent une réponse auto-immune chez des individus génétiquement prédisposés, bien que les mécanismes précis liant les facteurs d’environnement à l’auto-immunité thyroïdienne ne soient pas jusqu’à présent bien compris. Cependant dans la propagation de l’auto-immunité antithyroïdienne, les preuves s’accomulent de la responsabilité principalement du facteur nutritionnel et de la pollution dans l’environnement des métaux, des productions chimiques (comme les organochlorés, les pesticides). Cette revue présente un aperçu des connaissances actuelles concernant les facteurs liés à l’environnement, leur lien à la génétique et leur impact sur le système immunitaire.

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Mots clés : Iode ; Sélénium ; Nutrition ; Pollution ; Auto-immunité antithyroïdienne

« Il y a un autre monde mais qui se trouve dans ce monde... »

Paul Eluard

Thyroid autoimmunity (TAI), the main clinical manifestations being Hashimoto’s thyroiditis (HT) and Graves’ disease (GD), is on the rise worldwide. It today affects at least 10% of the population of North America and Europe, while a recent geoepidemiological analysis found incidence of autoimmunity widely prevalent round the globe, considerably increasing morbidity and mortality among all these populations [1].

TAI has been attributed to a complex interaction between genetic and environmental factors whose precise mechanism, however, has yet to be fully elucidated [2,3]. There is strong evidence showing a genetic origin for TAI: e.g. monozygotic twins possess a higher concordance rate of disease than dizygotic twins, while a higher concordance rate of the aggregation of thyroid autoantibodies in first-degree relatives of patients with TAI has also been reported [4,5]. Nevertheless, since the concordance rate even with monozygotic twins amounts to only 50%, it is hypothesized that environmental factors are significantly involved in development of TAI [6].

Today the best characterized TAI susceptibility genes are the immunoregulatory genes, such as the human leukocyte antigen class II (HLA-DR) gene locus, cytotoxic-T-lymphocytes antigen-4 (CTLA-4), protein tyrosine phosphatase-22 (PTPN22), which is a negative regulator of T cell recep-
tor signalling pathway, CD40, a major antigen presenting cell regulatory molecule, and the thyroid specific genes thyroglobulin and TSH receptor [7,8]. It is noteworthy that individual genes when assessed in a population study are likely to be weaker than when combined, thus exhibiting stronger genetic susceptibility to TAI [8]. It can hence be assumed that the interplay of genetic and environmental factors is of cardinal importance for the triggering of disease with the susceptibility genes contributing by 80% and environmental factors by 20% [2].

The recent association of metabolomics and genome-wide studies is equipping researchers with a more in-depth understanding of the pathomechanism of disease, while the link between nutrigenomics, proteomics and metabolomics is likely to provide a platform for prevention and enhanced treatment of TAI. Since there is abundant substantiation that epigenetics, nutrient intake and metabolism as well as climate and environmental exposures are dynamically interdependent, it is all but self-evident that AIT will demonstrate analogous genesis (Fig. 1). Meanwhile, it has been reported that certain epigenetics are dependent on specific food components, metals and pollutants for an individual’s susceptibility to type 1 diabetes mellitus or Crohn’s disease, these findings unmasking a pathogenetic association [9]. It is thus apparent that the environment may play a decisive role in modifying gene expression via epigenetic mechanisms thereby triggering autoimmunity [10].

This mini-review provides a brief assessment of the available data on environmental factors liable to initiate the autoimmune thyroid process in genetically susceptible individuals.

1. Environmental factors

Data on the environmental factors triggering TAI are as yet sparse. According to the available evidence, they include nutritive factors, pollutants, drugs and infections, while stress, tobacco and socio-economic milieu apparently also play a substantial role [11,12]. Table 1 presents the environmental factors involved in promoting TAI.

### Table 1
Environmental factors triggering thyroid autoimmunity.

<table>
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<tr>
<th>Nutrients</th>
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1.1. Nutritive factors

1.1.1. Iodine

Iodine is undoubtedly the most solidly established factor in onset of TAI. While a daily intake of about 150 μg is required for thyroid hormone synthesis, an iodine overload exceeding an intracellular concentration of 10 (−3) molar results in a paradoxical block of the organification of iodide (the so-called Wolff-Chaikoff effect) and of the iodine intrathyrocyte transport by the sodium-iodide symporter (NIS) [13]. This enables intracellular iodide to decrease below the critical level of 10 (−3) molar. However, in susceptible individuals the sodium-iodide symporter may fail to shut down, leading to hypothyroidism precipitated by prolonged excessive intracellular iodide concentration [13,14]. Iodide induced hypothyroidism has been reported in patients with a history of postpartum thyroiditis and after episodes of subacute thyroiditis [15].

Recently conducted experimental studies in a NOD.H2h4 mice model reported the multiple effects of excess iodine such as changes in the immunogenicity of the thyroglobulin, the upregulation of ICAM and the production of reactive oxygen species (ROS) as well as a link between iodine and autoimmune thyroiditis [16]. On the other hand, an association of the development of iodine-accelerated spontaneous autoimmunity in NOD.H2h4 mice with enhanced iodine organification in thyroglobulin (Tg) has recently been questioned [17].

Clinical studies carried out in various parts of the world support the linking of iodine with AIT. A good example is Greece, a longstanding iodine deficient country where, although implementation of a “silent iodine prophylaxis” program during the 1980s–1990s eliminated iodine deficiency and drastically reduced the incidence of goiter, it simultaneously provoked development of a high prevalence of AIT, especially in young women [18]. In China, it was shown that increasing iodine intake elevates the incidence of AIT and hypothyroidism, while a five-
year follow-up revealed that a baseline serum TSH of 1–1.9 mU/L is associated with the lowest incidence of thyroid function [19]. In Denmark, even a small increase in iodine intake was accompanied by a moderate increase in the incidence rate of overt hypothyroidism [20]. These studies, together with many more undertaken around the world, underline the importance of monitoring and adjusting iodine intake within the recommended levels as an efficient preventive measure [21], since even minor variations of intake among populations are associated with high risk of thyroid disease.

1.1.2. Selenium

Selenium is of vital importance for human health. When inserted in the form of the genetically encoded amino acid selenocysteine in the proteome, it characterizes the selenoproteins, such as glutathione peroxidases (GPxs) and deiodinases [22]. Selenium thereby potentiates the synthesis of thyroid hormones and optimizes function of the thyroid gland [22,23]. Based on evidence showing that selenium deficiency decreases the expression of these enzymes, which are highly involved in cellular antioxidative defense systems and redox control, thus impairing thyroid hormone synthesis, selenium supplementation has been undertaken in the forms of both selenomethionine and selenite and also in diet, with reports of a positive effect onAIT [24,25].

Selenium deficiency is also a risk factor for celiac disease which often displays an increased prevalence in patients with autoimmune thyroiditis and vice versa [26,27]. Due to resultant selenium malabsorption, it promotes gastrointestinal GPx malfunction leading to reduced apoptosis of the cells affected by oxidative stress, reiteration of the inflammation and aggravation of the mucosa lesions [27]. In the active form of celiac disease, overexpression of interleukin-15 (IL-15) occurs which, via effector mechanisms, may activate T helper 1 cytokine sustain gastrointestinal inflammation and promoteAIT.

Although the mechanisms via which selenium confers a positive effect inAIT are not as yet well known, a recent study has considerably added to our current knowledge. In an iodine-inducedAIT NOD.H2h4 mice model investigating the effects of selenium administration on the percentage of regulatory T cells (Treg) and expression of Foxp3 mRNA, it was shown that mice receiving selenium had reduced anti-Tg titers and reduced lymphocytic infiltration in the thyroid as compared with untreated mice [28]. Selenium treatment restored the depleted CD4(+)CD25(+)T cells in mice withAIT by increasing the expression of Foxp3 mRNA, this suggesting a potential thyrroprotective mechanism of selenium inAIT.

1.1.3. Iron

Iron is important for thyroid hormone synthesis as it catalyzes the activity of heme-dependent thyroid peroxidase, while iron deficiency results in impaired thyroid function and blunts the efficacy of iodine intake [29]. Combined deficiency of various trace elements, e.g. iron, selenium, copper and zinc, has been associated with goiter in children [30]. Moreover, a negative correlation of serum zinc with thyroid volume and TSH and a positive correlation between thyroid antibody levels and zinc have been reported [31].

Furthermore, ferritin, the marker of iron storage in the liver, has been implicated in autoimmunity [32]. Ferritin genes expression is stimulated by cytokines, while thyroid hormones and insulin regulate ferritin synthesis at the mRNA level [32]. Ferritin is likely to be increased in thyroid inflammatory diseases and decreased in overt hypothyroidism.

1.1.4. Vitamins

Certain vitamins, especially B12 and D, have been implicated in development of TAI. Pernicious anemia (PA), a macrocytic anemia caused by vitamin B12 deficiency, is associated by up to 40% with TAI and other autoimmune disorders [33]. While the HLA-DR genotype points to a genetic susceptibility, PA is also associated with atrophic gastritis, hypergastrinaemia and iron malabsorption.

Vitamin D deficiency has been associated with an increased incidence of autoimmune diseases, including TAI. The vitamin D receptor (VDR), which is expressed in cells of the immune responses, macrophages, T- cells and B-cells, enhances innate immunity and regulates the adaptive immunity system [34]. The ability of the VDR to activate immunological tolerance of T cells and promote the development of suppressive T cells (Treg) offers a potential agent to manipulate the tolerogenic properties of T cells [35]. These reports, among many more, highlight the potential application of a synthetic VDR agonist that may in future be applied, due to its anti-inflammatory and immunomodulatory properties in the treatment of autoimmune diseases [36].

1.2. Irradiation

There is some evidence that internal irradiation as radioiodine therapy for toxic goiter or autonomous adenoma in genetically susceptible individuals may induce Graves’ disease. On the other hand, a reported association between TAI and external irradiation is apparently dose-response related and, in any case, awaits further validation [12].

1.3. Pollutants

Observations by health professionals in numerous parts of the world are increasingly bringing pollution, among the various factors thought to trigger TAI, into the spotlight of scientific interest. Recently, a study in Brazil assessing the prevalence of HT and thyroid antibodies in residents of an area surrounding a petrochemical complex reported higher incidence of both HT (9.3%) and anti-thyroid antibodies than in the control area of Sao Paulo [37]. Although these findings were at variance with those of another study that found no difference in the prevalence of TAI in the urban area neighboring the petrochemical complex as compared with the control area, the above negative findings linking TAI risk with living in the vicinity of petrochemical industries requires further investigation [38]. There is also increasing concern as regards the possible linkage between chronic exposure to both solvents (benzene) and air pollutants (carbon monoxide) with thyroid and respiratory functioning. In
a recent study investigating the effects of long-term exposure to benzene and carbon monoxide in a group of non-smoking petrol station attendants, marked increase in T4 and FT4 and decrease in TSH and T3 serum levels were detected: this underscores the need, long corroborated by the well-known deleterious effects of these compounds on respiratory functioning, for urgent technological upgrading of gasoline station installations for the prevention of this environmental disease burden among filling station workers [39].

The worldwide rise in industrial activities, these often accompanied in developing countries by lax regulation has exacerbated the threat of organic pollution. Increased thyroid volume, presence of thyroid antibodies and elevated levels of polychlorinated biphenyls (PCBs) as well as impaired fasting glucose were detected in 137 females and 94 males, aged 21–35 years, in an area in Slovakia contaminated by organochlorines (OC) [40]. When the findings were compared with the younger persons’ parents’ generation who showed the same rate of adverse effects, the hypothesis was drawn that the OC body burden in the young adults was in fact a consequence of exposure to high levels of OC undergone by their mothers during the offspring’s prenatal and perinatal life.

In another study undertaken in East Slovakia, it was shown that fish from waters in the surrounding region that are consumed by the local population are becoming the prime source of ingested PCBs and pesticides, this leading to rising incidence of goiter and autoimmunity [41]. The exact mechanism involved remains unclear; however, in an experimental study assessing thyroid function in Sprague-Dawley rats after exposure to Aroclor (PCBs group), distinct histopathological changes, such as hyperplasia of epithelia in follicles, reduction of colloid content and lymphocytic infiltration into the perifollicular areas, were observed [42]. In parallel, the decreased FT3 and FT4 and the increased TSH serum concentrations and TPOAB titers indicated that PCBs affect thyroid functioning by inducing autoimmunity.

1.4. Drugs

Several drugs have been reported to damage thyroid functioning as a side effect of their application [43]. Drugs containing iodine may induce or exacerbate TAI in susceptible persons. Amiodarone is an iodine-rich compound widely applied for the treatment of tachyarrhythmias which typically induces an increase in T4 and rT3 and a decrease in T3 serum concentrations by inhibiting 5’deiodinase activity [44]. The drug may cause both hypothyroidism and hyperthyroidism, the latter presenting a major therapeutic challenge [45]. Recently, an international survey among members of the European Thyroid Association revealed the many uncertainties that remain concerning diagnosis and treatment of amiodarone-induced thyrotoxicosis [46].

Lithium which is widely used in patients with bipolar disorders induces goiter and hypothyroidism (20%) and increases TAI in susceptible individuals [47].

Interferon-gamma (IFN-γ) inducible CXC chemokines may play an important part in triggering autoimmunity in susceptible patients treated with IFNγ. It has been proposed that glandular epithelial cells may modulate the autoimmune process via production of chemokines which cause migration of Th1 lymphocytes into the gland, while IFN-γ secreted by lymphocytes further stimulates chemokines release by follicular cells [48].

1.5. Pregnancy

Pregnancy per se is an immunosuppressive state and should not be considered as a risk factor for TAI. Pregnant women with high TPOAB usually exhibit a decrease of the antibodies titer. However, postpartum has been associated with occurrence of TAI which is thought to be caused by microchimerism [12,49].

1.6. Infections

Infections have been implicated in triggering autoimmunity and especially TAI. Viral, bacterial and parasitic infections are known to induce autoimmune disease mainly via the mechanism of molecular mimicry [50]. The molecular mimicry model has been postulated as being a mechanism via which microbial antigen could ignite autoimmunity in susceptible persons due to its structural similarity to an autoantigen of the host: it could thus constitute a paradigm of interaction of environmental factors and genes [50]. The same mechanism that generates the autoimmune response to infectious invasion may well apply to the host response to vaccination [51].

Despite the lack of prospective epidemiologic studies, some evidence exists that infectious agents may trigger autoimmunity. For example, chronic hepatitis C virus (HCV) infection as well as Interferon-alpha (IFNα) therapy for HCV have both been connected with high incidence of clinical and subclinical autoimmune thyroiditis [14]. However, the mechanisms causing thyroid inflammation remain to be fully elucidated. Recently, three cases of Graves’ disease concomitantly presented with infectious mononucleosis were described, leading to the hypothesis that Epstein-Barr virus may be an important factor in the onset of Graves’ disease [52].

In another investigation studying sera from pregnant women, it was shown that prior infection with Toxoplasma gondii (Tg) elevates TPOAB and, although the results need further substantiation, a bystander effect of Tg in the enhancement of TPOAB response has been postulated [53]. However, it should be stressed that studies have failed to provide any confirmation of a direct link between viral infection and Hashimoto’s thyroiditis, only circumstantial evidence being cited for this [54].

Yersinia enterocolitica which has been linked to Graves’ disease was shown to produce a lipoprotein that reacts with TSH receptor (TSHr), thus functioning as a trigger of the autoimmune process [55]. This LP is characterized and cloned from YE and exerts considerable immunomodulatory effects, including the induction of antibodies that can cross-react with the TSHr and lead to breakdown of self-tolerance to TSHr [55].

1.7. Stress

With regard to stress, again there is only circumstantial evidence that this state may contribute to the onset of TIA, the
observed link between stress and Graves’ disease being the best paradigm [56,57]. A mechanism of stress that might trigger autoimmunity has not been fully established; however, it has been postulated that stress acts as an immune-modulator by affecting directly or indirectly the immune system via the nervous and the endocrine systems, thereby triggering autoimmunity in susceptible persons [57,58].

1.8. Lifestyle

1.8.1. Smoking

Tobacco smoke contains several potent goitrogens which interfere with NIS, TPO and dual oxidase (DUOX) activity, rendering smoking a major risk factor for thyroid disease. In a cross-sectional comparative population study organized in two areas with different iodine intake in Denmark, there was a negative association between smoking and the presence of thyroid antibodies in serum [59]. In a prospective study of 521 euthyroid women who were relatives of patients with TAI, environmental factors contributing to occurrence of thyroid antibodies were evaluated [60]. It was shown that the five-year probable time-span for conversion to TPOAB was 20.1% and that discontinuation of smoking is related to an increased risk for occurrence of TPOAB [60].

In contrast, tobacco smoking may develop thyroid-associated ophthalmopathy in patients with Graves’ disease and smokers receiving radiiodine have the highest incidence of deterioration or recurrence of this disorder [61].

Second-hand smoke (SHS) exposure disrupts thyroid function and induces inflammatory stress by increasing IL-1beta which impairs thyroid hormone synthesis and iodine uptake [62]. It is evident that, as SHS exposure disrupts human biological systems via thyroid impairment, preventive and educational measures should urgently be undertaken to protect against SHS via radical reduction of smoking.

1.8.2. Obesity

There is increasing evidence that obesity affects thyroid function via dysregulation of the pituitary-hypothalamic unit and adipose tissue, and that additionally, through leptin, it triggers thyroid autoimmunity. A cross-sectional study performed in 165 obese individuals showed that obesity increases susceptibility to develop TAI and that leptin apparently plays a major role in this process [63]. However, these findings are inconclusive and require further confirmation.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

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