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Environmental Issues Altering Thyroid Functions

Pallavi Mishra[1]
[1]Department of Home Science, NSPS Government PG College Magraha, Mirzapur (U.P.)

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Abstract

Autoimmune thyroiditis, of which Hashimoto thyroiditis represents the most frequent form, is an inflammatory state of the thyroid gland that results from the interaction between genetic variants that promote susceptibility and environmental factors. High iodine intake, selenium deficiency, pollutants such as tobacco smoke, infectious diseases such as chronic hepatitis C, and certain drugs are implicated in the development of autoimmune thyroiditis, primarily in genetically predisposed people. Long-term iodine exposure leads to increased iodination of thyroglobulin, which increases its antigenicity and initiates the autoimmune process in genetically susceptible individuals. Selenium deficiency decreases the activity of seleno proteins, including glutathione peroxidases, which can lead to raised concentrations of hydrogen peroxide and thus promote inflammation and disease. Such environmental pollutants as smoke, polychlorinated biphenyls, solvents and metals have been implicated in the autoimmune process and inflammation. Environmental factors have not yet, however, been sufficiently investigated to clarify their roles in pathogenesis, and there is a need to assess their effects on development of the autoimmune process and the mechanisms of their interactions with susceptibility genes.

Keywords- Autoimmune thyroiditis, environmental factors, selenium deficiency, polychlorinated biphenyls, pathogenesis,

Introduction

Environmental agents interfere with thyroid function at multiple sites, including thyroid hormone synthesis, thyroid hormone metabolism and excretion, and thyroid hormone action [1-4]. Most of these agents reduce circulating thyroid hormone levels or impair thyroid hormone action, although some may influence the pituitary and thyrotropin (TSH) secretion, or even be partial thyroid hormone receptor agonists. Several environmental agents interfere with iodine uptake. For these agents, low iodine intake increases susceptibility and adequate iodine intake is recommended to reduce their effect [3-5]. The thyroid can compensate, continue to produce a normal amount of thyroid hormone despite disruption, in response to some of these agents by increasing serum TSH [3-5]. The success of this compensation can be assessed in the adult based on markers of thyroid hormone action, but is much more difficult to determine during fatal development and in infants and children. Brain development is the best-characterized pathway that is thyroid hormone dependent and vulnerable to thyroid hormone disruption [6]. Local thyroid hormone activation and timing of availability of triiodothyronine (T3) is critical in brain and sensory development. Agents that interfere with thyroid hormone signalling during this period are the most difficult to detect and quantitate. A significant focus in clinical thyroid disease is to detect and evaluate thyroid disease at the earliest stages [7]. Recent efforts in assessing the impact of environmental agents that disrupt thyroid function have focused on identifying the earliest and subtle effects [8].

Assessing the Impact of Environmental Agents on the Thyroid

The ideal study of the impact of a thyroid toxicant matches a direct measure of exposure in an individual to their thyroid function. These findings are best interpreted with knowledge of the factors that can influence thyroid function, including thyroid autoantibody status, iodine intake, smoking history, family history of autoimmune thyroid disease, pregnancy, and use of medication. In most studies, these data are not all available. Thyroid autoimmunity should be considered as a contributing factor to thyroid changes seen with

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environmental agents. These studies are also relevant to understanding the pathogenesis of autoimmune thyroid disease and the potential role of environmental agents in this process.

Autoimmune Thyroid Disease

The common model of the onset of autoimmune thyroid disease involves an underlying genetic predisposition and a trigger(s) that initiate the cascade of events and sustain the process, culminating in thyroid hypofunction or hyperfunction. This process has been extensively studied and described [9]. It has been estimated, based on twin studies [10], that 70%–80% of susceptibility to autoimmune thyroid disease is on a genetic basis. The specific genes involved include human leukocyte antigen-DR3, cytotoxic T lymphocyte-associated factor 4, CD40, protein tyrosine phosphotase-22 gene, thyroglobulin (Tg), and TSH receptor [9]. The identified genetic association with autoimmune thyroid diseases confers susceptibility to Graves' disease, Hashimoto's disease, or both. The remaining 20%–30% contribution to the onset of autoimmune thyroid disease is thought to be due to environmental exposures or triggers. There are several exposures that have been identified and proposed, both from human and animal studies [11-14]. These include infections, life stress, iodine intake, smoking, medications such as amiodarone and interferon, radiation, and environmental toxicants (Table 1). A prospective study of 790 women with first- or second-degree relatives with proven autoimmune thyroid disease determined the strongest predictors of a thyroid event, overt hypothyroidism or hyperthyroidism [11]. Those who developed a thyroid event had, at baseline, a higher TSH, higher thyroid peroxidase (TPO) antibody levels, and more relatives with Hashimoto's disease [11]. None of the triggers of autoimmune thyroid disease that were studied directly contributed to the development of a thyroid event. Geographic susceptibility has also been shown for some autoimmune diseases, but thyroid autoimmunity occurs throughout the world and does not have a distinct geographic distribution [15]. This study did not look at iodine intake in specific regions, however, which would be expected to impact the incidence of autoimmune thyroid disease in a specific area as described below.

Table 1. Partial List of Environmental Agents That Interfere with Thyroid Function.

Agent	Example of sources	Mode of action	Associated as a trigger or accelerating autoimmune thyroid disease
PCBs	Found in coolants and lubricants, multiple cogeners, lipophilic	TR agonist/antagonist, can alter levels of T4 and TSH	Possible increase in TSH, thyroid autoantibodies, thyroid volume
Organochlorine pesticides	Used as pesticide on crops	Induce hepatic UDPGTs and glucuronidate T4, accelerating metabolism	No human studies establishing association
PBDEs	Found in flame retardants	Bind to TRs, displaces T4 from binding proteins	Increase in HT in some studies

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BPA	Used in plastic bottles	Antagonize TR	No human studies establishing association
Perchlorate, thiocyanate	Rocket fuel, fertilizer, smoking	Inhibits iodine uptake	No human studies establishing association
Triclosan	Antibacterial in soaps	Reduce serum T4, disrupt amphibian development	No human studies establishing association
Isoflavones	Soy products	Inhibits TPO activity	Possible increase in HT

PCBs, polychlorinated biphenyls; TR, thyroid hormone receptor; T4, thyroxine; TSH, thyrotropin; UDPGTs, uridine diphosphate glucuronyltransferase; PBDE, polybrominated diphenylethers; HT, Hashimoto's thyroitidits; BPA

The relative importance of these environmental factors in the development of autoimmune thyroid disease is not established. Only a few prospective studies have followed at-risk individuals to determine the relative importance of these exposures. The environmental factors most closely associated with susceptibility to autoimmune thyroid disease include radiation, iodine intake, and environmental toxicants. The mechanism of action for most thyroid toxicants is not established, but this information is not required to make an association of exposure with thyroid dysfunction. Although there are limited data in this area to translate to the management of individual patients, there are findings that can contribute to a strategy of risk reduction.

Radiation

Radiation is perhaps the best characterized environmental exposure linked to effects on the thyroid. The most common thyroid manifestation of radiation is hypofunction, as well as thyroid nodules and thyroid cancer. Autoimmune thyroid disease has been linked to therapeutic medical radiation [20–22], as well as environmental radiation exposure [23–28]. Both the atomic bomb detonations in Japan [24] and nuclear contamination from the Chernobyl nuclear power plant accident [27] have been associated with an increased risk of autoimmune thyroid disease. This association, however, has not been a consistent finding in all studies, with several showing no effect [24, 28]. Radiation exposure from a nuclear incident generally occurs at a known time, and an approximation of the exposure can be obtained from the location of the exposed individual and content and patterns of radioactive release and fallout. Significant variation in individual effects of radiation on the thyroid is likely, however, due to factors such as age, gender, the presence of thyroid autoantibodies, dietary iodine intake, use of dairy products where iodine isotopes are concentrated, and variations in weather patterns and food and water intake.

Iodine Intake

It is well known that at a population level thyroid antibodies and autoimmune hypothyroidism are more common in iodine-replete areas than in iodine-deficient areas. The most recent evidence supporting this statement comes from Denmark. The prevalence of TPO-Ab before and after mandatory iodization of salt was 14.3% and 23.8%, respectively [10], and the incidence of overt hypothyroidism increased from

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38.3/100.000 per year at baseline to 47.2/100.000 per year 5 to 7 years after iodine fortification of salt [11]. Voluntary iodine prophylaxis in a small Italian community also increased prevalence of TPO-Ab (12.6% vs. 19.5%) and hypothyroidism (2.8% vs. 5.0%) 15 years later [12]. At an individual level, one should follow the World Health Organization recommendation of a daily iodine intake of about 150 µg.

Genetic Background

Given that 70%–80% of susceptibility to autoimmune thyroid disease is based on genetics, individuals with a personal history of autoimmune disease or family history of autoimmune thyroid disease are the most susceptible. Those with a sibling that has autoimmune thyroid disease are at increased risk, especially strong for Hashimoto's thyroiditis [46]. Well-established risk factors for autoimmune thyroid disease include being female and older age. In a prospective study, the higher the serum TSH and antithyroid antibody levels, and the more relatives with thyroid disease, the greater risk of progression of thyroid disease [11]. Elevated antithyroid antibodies were associated with increased risk of autoimmune thyroid disease in long-term follow-up in the Whickham survey [47]. Although reducing exposure risk for autoimmune thyroid disease can be applied to any individual, those in the high-risk categories based on family history are especially susceptible.

Vitamin D

Low vitamin D levels have been identified as risk factors for various autoimmune diseases (like type 1 diabetes, rheumatoid arthritis, hypothyroidism and multiple sclerosis). There have been many cross-sectional studies evaluating an association between vitamin D blood levels and AITD, with conflicting results.

Selenium Deficiency

The thyroid gland is an organ with one of the highest levels of selenium, containing a large number of selenoproteins, which indicates the great importance of selenium in the synthesis, activation, and metabolism of thyroid hormones This element also plays a vital part in the proper functioning of the immune system. These properties are of particular significance in the pathogenesis of autoimmune thyroiditis, the development of which may be predisposed by chronic selenium deficiency. The level of selenium in the body is significantly influenced by the amount of this trace element in the soil in the inhabited area, as well as the supply of selenium in the diet, which was demonstrated in a study conducted by Qian Wu et al., in which selenium deficiency was almost twice as common in people living in an area with a lower selenium intake compared to a population living in an area with an adequate selenium intake. Moreover, the number of new cases of AIT that were diagnosed in the area with the lower selenium intake was three times higher in comparison with that in the area with an adequate selenium intake, which indicates a significant influence of selenium deficiency on the pathogenesis of AIT(49)

Viral Infections

Another environmental factor that may have a potential impact on the development of autoimmune thyroiditis is viral infections. It is assumed that infections caused by viruses may be involved in triggering AIT thanks to their molecular mimicry, which enhances autoimmune responses. Many studies have been carried out to check the relationship between viral infection and the further development of Hashimoto's disease, but only a few of them were carried out on a large group of people, and the results were not clear in all of them, which indicates the need to conduct further research. Of all the viruses potentially linked to the development of AIT, Epstein–Barr Virus (EBV), human parvovirus B19 (PVB19), human herpesvirus 6A (HHV-6A), and severe

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acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are the ones considered most likely to influence the development of the condition.

Cigarettes

Cigarette smoking, as well as cessation of smoking, have been linked to the onset of autoimmune thyroid disease. The increase in risk of the onset of autoimmune thyroid disease with cessation of smoking may be useful in monitoring susceptible patients who stop smoking for the myriad health benefits. For example, cessation of smoking may be associated with weight gain, and hypothyroidism should be considered as a cause. Cigarette smoke contains cyanide, which is metabolized to thiocyante, and can interfere with iodine concentration in the thyroid and in the lactating breast [2].

Pregnancy and the postpartum period

The transition from immune suppression to release from suppression is associated with the onset of several autoimmune diseases; postpartum thyroiditis is the most common. The impact of fatal cells on maternal immune response, fatal microchimerism, is increasingly recognized as a trigger for thyroid autoimmunity [12].

Medications

Medications associated with the onset of autoimmune thyroid disease include lithium, amiodarone, interferon α, interleukin 2, campath-1h, and highly active anti-retroviral therapy [2, 13]. For most of these medications, patients at greatest risk for developing autoimmune thyroid disease are those with previous thyroid autoantibody positivity. Some medications, such as lithium, may not trigger autoimmunity, but accelerate the autoimmune process by interfering with thyroid function. Thyroid function testing and measurement of TPO antibodies should be considered in patients before beginning these medications. Medications differ in their mechanisms of stimulating thyroid autoimmunity, as well as the relative effect on promoting hypothyroidism or Graves' disease [12].

Toxicants

Most municipal water sources are now closely monitored for a range of toxicants, including those that affect the thyroid. Individuals using well water should ensure that it is tested regularly for contaminants. Reduction of exposure to toxicants in the environment and occupational settings, including agents that affect the thyroid, is an ongoing effort involving many groups and agencies [1-6].

Stress

Stress as a provocative factor in the pathogenesis of Graves disease is well known. Several case-control studies report a higher frequency of stressful life events in the year preceding the diagnosis of Graves' hyperthyroidism relative to controls [46-49]. These studies were all retrospective in nature, and therefore the obtained evidence is at best circumstantial. Stress exposure in subjects developing Hashimoto's thyroiditis has hardly been studied. The Amsterdam AITD cohort assessed recent life events (both pleasant and unpleasant) and daily hassles by means of annual questionnaires during the 5-year follow-up. Two nested case-control studies in the cohort did not find any association between stress exposure and de novo occurrence of TPO-Ab or the development of overt autoimmune hypothyroidism [50-54].

Conclusions- In conclusion, various environmental factors may influence the development of autoimmune processes in thyroid tissues. Excessive iodine consumption should be highlighted as a risk factor. The correct intake of iodine in the daily diet may prevent the development of AIT.

Furthermore, vitamin D deficiency is an important but still unclear risk factor for AIT. More research should be conducted to reveal the relationship between vitamin D deficiency and the development of AIT. However, proper vitamin D intake appears to be a protective factor for the development of AIT.

Selenium deficiency may also contribute to the development of autoimmunity. Studies have shown that selenium supplementation can improve thyroid function in terms of AIT. However, more research on larger populations is necessary. Research also confirms the relationship between viral and bacterial infections and the development of AIT, which may result from molecular mimicry Interestingly, the autoimmune process of the thyroid gland, which can be influenced by many different factors, can even be linked to climate change and weather factors. An increased predisposition to AIT appears to occur in populations living in harsh and cold parts of the world, which may shed new light on the occurrence of AIT in the context of ongoing climate change and global warming.

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