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Effect of the Genetic and Environmental Factors on Hashimoto's Thyroiditis

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Abstract:
This review explores the complex interplay of genetic and environmental factors contributing to its development. Genetic predisposition, particularly involving HLA genes and immune regulatory genes, plays a crucial role. Environmental factors such as smoking, iodine intake, infections, vitamin D deficiency, and exposure to radiation can significantly influence disease onset and progression. Furthermore, lifestyle factors including pregnancy, gluten intake, and gut microbiota dysbiosis have been implicated in the development or exacerbation of HT. This review highlights the importance of considering both genetic and environmental factors in understanding the pathogenesis of HT and developing effective prevention and treatment strategies.

Keywords: Hashimoto's thyroiditis, AITD, Genetic factors, Environmental factors, Autoimmunity
Note: The review is based on a PhD dissertation.

Introduction

The autoimmune thyroid disease (AITD), a class of organ-specific autoimmune illnesses marked by lymphocyte infiltration into thyroid gland tissue, includes Hashimoto's thyroiditis (HT) (1). Dr. Hakaru Hashimoto was the first person to diagnose Hashimoto's illness in Japan in 1912. He studied the thyroid glands and recorded the cases of four middle-aged women who had had thyroidectomies because of symptoms of compression (2,3). The precise mechanisms of etiology and pathogenesis of Hashimoto's thyroiditis are not properly understood, and the first stage of this disease involves the accumulation of lymphocytes, plasma cells, autoantibodies, and other immune mediators such as cytokines, Chemokines, Complement proteins, and Reactive oxygen species (ROS) (4). The incidence of HT is estimated to

be 0.3-1.5 cases per 1000 people, and the prevalence of the disease is more common in women than in men, with a female to male predominance of 7-10:1(5), the exact reasons for this female predominance are not fully understood, but several factors likely play a role such as female sex hormone may increase the susceptibility to autoimmune diseases (6), Pregnancy and postpartum period can trigger or exacerbate autoimmune conditions in some women (7), and Women experience significant hormonal fluctuations throughout their lives, which can affect the immune system (8) . The most common laboratory indicates an increase in thyroid-stimulating hormone (TSH) and a decrease in free thyroxine 4 (fT4) levels, accompanied with an increase in antithyroid peroxidase antibodies (Anti-TPO) (9). A study revealed that 7.5% of women exhibited elevated levels of thyroid stimulating hormone (TSH), while 10.3% tested positive for the presence of anti-thyroid peroxidase antibodies (Anti-TPO). Goiter was found to be present in 15% of the female population (10), and based on the positive results of laboratory testing in women regarding the presence of autoantibodies for thyroid, it has been observed that around 10% of the population exhibits Hashimoto's thyroiditis (11).

Factors Risk of Hashimoto's thyroiditis

Genetic factors

Genetic factor plays a critical role in the development of Hashimoto's disease, an autoimmune disorder characterized by thyroid gland inflammation. The research indicates that specific genetic predispositions associated with the disease, particularly related to human leukocyte antigens (HLA) and various immune regulatory genes (*CTLA-4*, and *PTPN22)*, significantly influence susceptibility to HT (12). The genetic factors believed to have a significant role in the development of Hashimoto’s thyroiditis are the major histocompatibility complex (MHC), cytotoxic T-lymphocyte antigen-4 (CTLA-4), and HLA (13,14). The relationship between Hashimoto’s thyroiditis genetics and the HLA gene has been examined by using serotyping of the HLA and DNA sequencing of oligonucleotides. Variants in HLA-DR, particularly HLA-DR4, are strongly associated with HT, indicating a genetic susceptibility linked to immune response regulation (15). HLA genes of different categories have been observed to exhibit varied levels of association with HT in various race groups. Hashimoto’s disease in Asian people is associated with both the HLA class one and class two genes, whereas in Caucasians, only the HLA class 1 gene is connected to

Hashimoto's disease (16). The development of autoimmune thyroid diseases (AITD) is determined by genetic factors affecting the immune response, and genes such as CTLA-4 (cytotoxic T lymphocyte-associated factor 4), PTPN22 (protein tyrosine phosphatase 22), and FOXP3 (Forkhead box P3) are implicated in the autoimmune process, affecting T cell regulation and tolerance to thyroid antigens (17,18). It is thought that the development of Hashimoto's illness and other autoimmune diseases, including Graves' disease, begins with the loss of CTLA4, which is crucial for maintaining immunological tolerance inside the body (19,20). The probability of developing HT is also influenced by variations in thyroid-specific genes linked to the thyroglobulin and TSH receptor genes (15).

Environmental Factors

Many environmental factors as we see it in Figure 1 may trigger autoimmune disorders in patients with genetic predisposition, and exposure to various environmental agents has been linked to an increase prevalence of Hashimoto's disease, and most researchers have not conducted mechanistic studies on how these environmental factors can induce autoimmune thyroid diseases (AITD) (21,22).

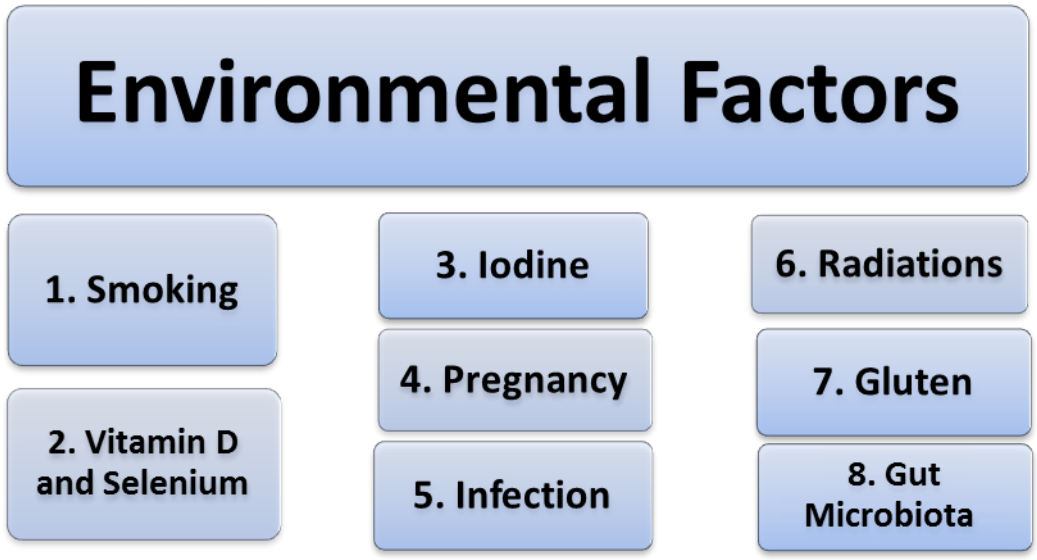

Figure (1): The Environmental Factors That Affect Hashimoto Thyroiditis

Smoking

The association between smoking and AITD (autoimmune thyroid disease), as demonstrated by epidemiological studies, has become well recognized in the past decade. In several studies shown the levels of thyroid hormones have to be greatest in smokers than non-smokers, and there are several factors determine the connection between cigarette smoking and anti-TPO antibodies (23,24). The researcher found that the smoking may protect against the development of thyroid peroxidase antibodies (TPO-Ab), which are linked to Hashimoto's hypothyroidism, and suggests that smokers might have a lower risk of developing Hashimoto's thyroiditis compared to non-smokers (23). The researchers suggest that smoking can induce changes in thyroid function tests, such as a decrease in TSH and an increase in thyroid hormones, and found elevated in concentration of TPO antibodies and thyroglobulin antibodies (Tg), and daily smoking number and long-term smoking decrease serum TSH and TPO antibodies levels, and smoking plays a significant role in the development of thyroid dysfunction (25,26)

According to a recent study, stopping smoking is linked to an increased risk of developing autoimmune hypothyroidism and new-onset thyroid autoimmunity, particularly in the first year after quitting. After receiving effective treatment for Graves' illness, up to 20% of individuals may develop spontaneous hypothyroidism as a result of quitting smoking (27).

Iodine

Iodine is an essential element necessary for the manufacture of thyroid hormones. The research has demonstrated that iodine deficiency detrimental effects to individuals is significantly more severe than the detrimental effects of excessive iodine consumption (28). The high iodine intake has been associated with an increased frequency of autoimmune thyroiditis, including Hashimoto's thyroiditis, and excess iodine can lead to hypothyroidism, potentially triggering autoimmune responses in predisposed individuals (29).

The studies have shown that iodine supplementation can influence the levels of thyroid antibodies. For instance, weekly high-dose iodine supplementation significantly increased antithyroglobulin (Tg) and antiperoxidase (TPO) antibody levels, whereas daily low-dose iodine did not show a significant increase in antibody titers, while in patients with Hashimoto's thyroiditis, a combination of hormone therapy and low-dose iodine supplementation has been shown to reduce Tg and TPO antibody levels, suggesting a potential therapeutic strategy for managing Hashimoto's thyroiditis (30).

In recent studies have demonstrated that iodine is the main factor responsible for triggering Hashimoto's thyroiditis. Thyroid antibodies and autoimmune hypothyroidism are more prevalent in places with sufficient iodine levels compared to areas with iodine deficits, as widely recognized Researchers provided the latest evidence to support this claim, showing a considerable increase in the incidence of thyroglobulin peroxidase antibodies (TPO-Ab) following compulsory salt iodization. Furthermore, the incidence of hypothyroidism increased with the implementation of salt iodization (31,32).

The restricting iodine intake has been shown to improve thyroid function in patients with Hashimoto's thyroiditis. In cases of mild hypothyroidism due to Hashimoto's thyroiditis, iodine restriction alone has led to a significant recovery rate, with up to 78.3% of patients regaining euthyroid status, and the factors such as low initial serum TSH and high initial urinary iodine concentration have been identified as predictors for recovery from hypothyroidism following iodine restriction (33).

Infection

There is a connection between infections and the development of autoimmune thyroid diseases (AITD) that including viral or bacterial infections, which could be a risk factor for AITD. A link between thyroid autoimmunity and both IFN-α (Interferon alfa) and hepatitis C virus has been observed, and possible causes of the condition may involve the phenomenon of molecular mimicry, where viral antigens resemble self-antigens, as well as the release of proinflammatory substances linked to viral infection, which could potentially trigger the activation of self-reactive T-cells (34,35). According to recent research, it is suggested that both Covid-19 infection and its vaccines have the potential to trigger or aggravate autoimmune thyroid diseases (AITD) in patients who are in remission of their underlying thyroid condition (36). The researcher found *C. albicans* and *Lactobacillus* exhibit a greater prevalence in the saliva of both hyperthyroid and hypothyroid patients compared to the control group (37). The abundance and diversity of bacterial in patients with Hashimoto thyroiditis were significantly reduced, and the relative abundances of *Bacteroides*, *fecal Bacillus*, *Prevotella*, and *Lactobacillus* also decreased (38). Pregnant women with preeclampsia had a significantly lower abundance of *Prevotella*, *Porphyromonas*, *Varibaculum*, and *Lactobacillus* than pregnant women without this complication (39).

Vitamin D

The patients with Hashimoto's thyroiditis had significantly lower levels of vitamin D compared to healthy individuals. This suggests a potential link between vitamin D deficiency and HT. The severity of vitamin D deficiency was found to correlate with the duration of HT, meaning that the longer a person had HT, the more severe their vitamin D deficiency tended to be (40). Vitamin D have been linked to the progress of thyroid autoimmunity, and the patients with Hashimoto's disease often have a deficiency of vitamin D, and the research indicates that there is a link between low levels of vitamin D and an increased chance of developing HT and thyroid cancer. However, this risk can be reduced by supplementing with vitamin D (37,41,42). Vitamin D supplementation has been shown to improve thyroid function in HT patients by decreasing thyroid-stimulating hormone (TSH) levels and increasing free triiodothyronine (FT3) and free thyroxine (FT4) levels. A meta-analysis indicated that active forms of vitamin D, such as calcitriol, are more effective in reducing TPO-Ab levels compared to naive forms like vitamin D2 or D3, especially with treatment durations longer than 12 weeks (43).

Vitamin D is known to play a crucial role in immune function, potentially influencing the course of autoimmune diseases like HT by promoting immune tolerance and reducing inflammation (44,45). Studies have shown that vitamin D can inhibit the secretion of pro-inflammatory cytokines, which may lead to an improvement in the clinical picture of HT by shifting the immune response from a pro-inflammatory to a more balanced state (44). Vitamin D supplementation has been associated with a significant decrease in thyroid autoantibody titers, such as anti-thyroid peroxidase (TPO-Ab) and thyroglobulin antibodies (TG-Ab), which are key markers of HT (43,46)

Selenium

Selenium, an essential trace element, plays a significant role in the management of Hashimoto's thyroiditis, and crucial element in diet that has several pleiotropic effects, which including antioxidant and anti-inflammatory properties and has ability to enhance the production of thyroid hormones, and the researcher found that selenium was considered element of the enzymes that regulates thyroid hormones, which thyroid gland has the highest concentration of selenium per gram of tissue, selenium administration in patients with autoimmune thyroid diseases (AITD), such as Hashimoto's disease, appears to alter the inflammatory and immunological response (43,47). There is evidence indicating that a reduced intake of selenium may trigger the onset of Hashimoto's disease (5). Intake of Selenium

supplementation has been shown to significantly reduce thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TGAb) after six months of treatment, suggesting a beneficial effect on thyroid autoimmunity (48). In a study involving women with newly diagnosed HT, selenium supplementation led to a significant decrease in anti-thyroid peroxidase antibodies, which may stabilize thyroid function (49). Selenium treatment resulted in decreased TSH levels and increased antioxidant activity, which may benefit subclinical HT patients more significantly (50). Some studies report no significant changes in free and total thyroxine (fT4, T4) and triiodothyronine (fT3, T3) levels, indicating that selenium's impact on thyroid hormone levels may be limited (51).

Pregnancy

Hashimoto's thyroiditis is greatly impacted by pregnancy, mostly due to changes in the immune system and hormones. This may exacerbate autoimmune diseases like HT by causing changes in the mother's immune system, especially with regard to innate immunity (52). According to the study, more than half of women with Hashimoto's thyroiditis experienced an increase in their pregestational thyroid dosage in the postpartum period. Women who test positive for thyroid peroxidase (TPO) or thyroglobulin (Tg) antibodies in the first trimester of pregnancy are at risk for developing postpartum thyroiditis, and this is likely related to the degree of autoimmune thyroid dysfunction after childbirth and this result of the significant hormonal changes occur during pregnancy, particularly in the first trimester. These hormonal shifts can influence the immune system and potentially trigger or exacerbate autoimmune processes (53). The prevalent of thyroid autoimmunity in pregnant women is 2-17%, with associated risks such as miscarriage, preterm birth, and developmental issues in offspring, and women with Hashimoto’s disease have high risk of complications like gestational diabetes and postpartum thyroiditis (54).

Radiations

The individuals who have positive thyroid autoantibodies should be particularly cautious and alert for the development of autoimmune thyroid disease following medical radiotherapy (21). Overall, the thyroid gland has been found to be susceptible to radiation. Research has demonstrated that radiation exposure can lead to the development of not just malignant thyroid tumors, but also non-cancerous conditions such benign thyroid nodules (such

as Graves' disease and Hashimoto's thyroiditis) and non-autoimmune hypothyroidism (55).

Gluten

Gluten is a protein complex found in wheat and related grains, such as barley, rye and oat (36). The effect of gluten on Hashimoto's thyroiditis has garnered attention due to its potential role in autoimmune responses, the research show that gluten has been implicated in the immune response associated with HT that potentially leading to increased inflammation and thyroid dysfunction. Some Studies suggest that gluten may trigger autoimmune reactions, particularly in individuals with a predisposition to autoimmune diseases (56). Gluten-free diets have shown promise in reducing the levels of thyroid antibodies (anti-TPO and anti-Tg) and improved thyroid hormone levels, particularly in patients without celiac disease (57,58). Dietary modifications, including gluten-free diets, may enhance the expression of regulatory genes like foxp3, which are crucial for immune regulation in HT (59).

Gut Microbiota

The gut microbiota influences the absorption and metabolism of essential micronutrients necessary for thyroid function, such as iodine, selenium, and zinc. These nutrients are critical for thyroid hormone synthesis and conversion, and their deficiency can exacerbate HT symptoms (60,61). Alterations in gut microbiota can lead to impaired nutrient absorption, further affecting thyroid hormone levels and potentially worsening HT. Probiotic supplementation has shown promise in modulating gut microbiota and improving thyroid function, suggesting a potential therapeutic avenue for managing HT (61).

The gut microbiota plays a crucial role in regulating the host's immune system, which is pivotal in autoimmune diseases like HT. Dysbiosis, or the imbalance of gut microbiota, has been linked to the development of HT by affecting the TH17/Treg (helper type 17/Regulatory T) balance, which is crucial for maintaining immune homeostasis (62,63). The presence of specific bacterial species, such as increased Bacteroides and decreased Bifidobacterium, has been observed in HT patients, suggesting a direct link between microbiota composition and immune response in HT (64).

Conclusion

Hashimoto's thyroiditis is an autoimmune disease characterized by thyroid gland inflammation, primarily affecting women. While the exact etiology remains unclear, a complex interplay of genetic and environmental factors contributes to its development. Genetic predisposition, particularly involving HLA genes and immune regulatory genes, plays a crucial role in disease susceptibility. Environmental factors, such as smoking, iodine intake, infections, and vitamin D deficiency, can significantly influence disease onset and progression. Furthermore, pregnancy, radiation exposure, gluten intake, and gut microbiota dysbiosis have been implicated in the development or exacerbation of HT. While further research is needed to fully elucidate the intricate mechanisms underlying HT, understanding the interplay of these factors is crucial for developing effective prevention and treatment strategies.

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تأثير العوامل الوراثية والبيئية في الإصابة بالتهاب الغدة الدرقية الهاشيموتا

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مستخلص البحث:

تستعرض هذه المراجعة التفاعل المعقد بين العوامل الوراثية والبيئية التي تساهم في تطوره. يلعب الاستعداد الوراثي، لا سيما ما يتعلق بجينات HLA والجينات المنظمة للمناعة، دورًا حاسمًا. يمكن أن تؤثر العوامل البيئية مثل التدخين وتناول اليود والعدوى ونقص فيتامين (د) والتعرض للإشعاع بشكل كبير على ظهور المرض وتطوره. علاوة على ذلك، فإن عوامل نمط الحياة بما في ذلك الحمل، وتناول الغلوتين، واختلال توازن الكائنات الدقيقة قد يكون لها دور في تطور أو تفاقم التهاب الغدة الدرقية الهاشيموتا. تسلط هذه المراجعة الضوء على أهمية النظر في كل من العوامل الوراثية والبيئية في فهم مسببات في الإصابة بالتهاب الغدة الدرقية الهاشيموتا وتطوير استراتيجيات وقاية وعلاج فعالة.

الكلمات المفتاحية : التهاب الغدة الدرقية هاشيموتا، مرض الغدة الدرقية المناعي الذاتي AITD، العوامل الوراثية، العوامل البيئية، المناعة الذاتية

ملاحظة : هل البحث مستل من رسالة ماجستير او اطروحة دكتوراه ؟ نعم