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TRIGGER FACTORS OF HASHIMOTO'S HYPOTHYROIDISM: A LITERATURE REVIEW

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ABSTRACT

Hashimoto disease is one of the most frequently occurring autoimmune diseases, characterized by lymphocytic infiltration, destruction and scarring of thyroid tissue. It is reported several factors related on its pathogenesis. Among environmental factors smoking and alcohol have significant effects, both protective as well as for aggravating the disease, even though the precise nature of these effects are not clearly known. There are elevated levels of circulating antibodies against the thyroid proteins, mainly thyroid oxidase, thyroglobulin and thyroid stimulating hormone receptor, in patients with HT. Linkage and association studies in AITD identified several major genes that are relevant for the onset of AITD, including the thyroid-specific genes, thyroglobulin and thyroid-stimulating hormone receptor and also many immune-regulatory genes.

Keywords: Hashimoto's hypothyroidism, Autoimmune thyroid disease, environmental, Genetic factor

INTRODUCTION

Autoimmune thyroid disease (AITD) is a multifactorial disease in which autoimmunity against thyroid antigens develops against genetic background facilitated through wide range of environmental factors. The AITD encompasses a spectrum of conditions ranging from Hashimoto's hypothyroidism to Graves' hyperthyroidism **[1]**. Hashimoto (HT) disease is one of the commonest autoimmune diseases, characterized by destruction and scarring of thyroid tissue, lymphocytic infiltration and presence of antibodies to thyroid peroxidase and thyroglobulin **[2]**. The name "Hashimoto's disease" comes from Japanese Surgeon Dr. Hakaru Hashimoto, who in 1912 described this disease. The disease is more likely to affect women than men, aged 30–60, and the risk increases by getting older **[3]**. It is reported at any age and dysfunction of the gland may be clinically evident (0.1–2% of the population) or subclinical (10–15%). The HT is related to impairment of the immune system with excessive production of antibodies. Among environmental factors smoking and alcohol have significant effects, both protective as well as for aggravating the disease, even though the precise nature of these effects are not clearly known. There are elevated levels of circulating antibodies against the thyroid proteins, mainly thyroid oxidase, thyroglobulin and thyroid stimulating hormone receptor, in patients with HT. Linkage and association studies in AITD identified several major genes that are relevant for the onset of AITD, including the thyroid-specific genes, thyroglobulin and thyroid-stimulating hormone receptor and also many immune-regulatory genes. In this review we addressed many aspects of AITD including disease mechanisms, involved thyroid antigens, environmental factors and genetic factors based on an electronic search in PubMed and Google Scholar databases we focus on trigger factors of Hashimoto disease.

MATERIAL AND METHODS

The keywords used for the literature search for this review was peer-reviewed articles following keywords:"Hashimoto's hypothyroidism", "Autoimmune thyroid disease", "Environmental", "Genetic factor". The search was done and almost 88 abstract and papers collected which the keywords included in them. Among them, the papers were fit the criteria selected and available full-text articles read. Related articles were also scrutinized. Hand search was also driven. The search carried out using Biological Abstracts, Chemical Abstracts, and the data bank of the PubMed and Medline database updated to 2020. The references found in the search were then studied in detail.

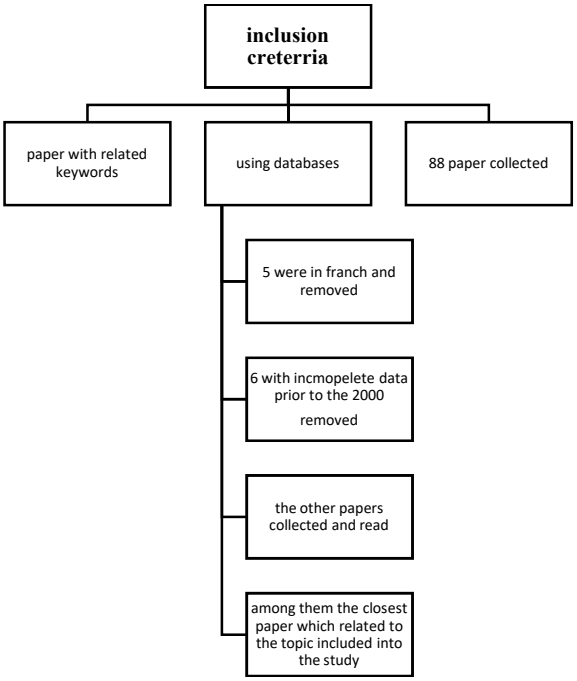

Diagram 1: The flow chart of the study

Hashimoto's hypothyroidism

Hashimoto's thyroiditis (HT), known as chronic lymphocytic thyroiditis and chronic autoimmune thyroiditis which is the most common autoimmune disease and cause of primary hypothyroidism in iodine-sufficient areas **[4]**. The HT has variety of histopathological and clinical entities which characterized through intrathyroidal lymphocytic infiltration. The HT patients can suffer from a several manifestations attended by other autoimmune disorders **[5]**. Moreover, HT increased risk of primary thyroid lymphoma and papillary thyroid cancer **[6]**.

Diagnose of HT

Diagnosis begins with a physical exam and medical history. A goiter, nodules, or growths may be found during a physical exam, and symptoms may suggest hypothyroidism. Health care providers will then perform blood tests to confirm the diagnosis. A blood test involves drawing blood at a health care provider's office or a commercial facility and sending the sample to a lab for analysis.

TSH test. The ultrasensitive TSH test is usually the first test performed. This test detects even tiny amounts of TSH in the blood and is the most accurate measure of thyroid activity available. Generally, a TSH reading above normal means a person has hypothyroidism.

T4 test. The T4 test measures the actual amount of thyroid hormone circulating in the blood. In hypothyroidism, the level of T4 in the blood is lower than normal.

Anti-thyroid antibody test. This test looks for the presence of thyroid autoantibodies, or molecules produced by a person's body that mistakenly attack the body's own tissues. Two principal types of anti-thyroid

antibodies are anti-TG antibodies, which attack a protein in the thyroid called thyroglobulin

Factors related to the HT

Several reports have been done, but the pathogenesis of HT remains unclear. There is an overall idea for interactions of genetic susceptibility, environmental factors, and immune disorders contribute to its development. Also, it is assumed there is equally important role of environmental factors in the disease pathogenesis **[7]**. Some type bacteria or virus accelerate the immune system to attack the thyroid. Also, genetic defect as well as female more commonly affected. Additionally, age, physiological (heart failure, emotional, congenital and etc.) and environmental factors are increased risk. Here we reviewed the possible factors.

Table 1

Box 1. Risk factors for autoimmune thyroid disease

Environmental
- Iodine consumption
- Smoking (possibly protective)
- Radiation
- Drugs (including biologic agents)
- Alcohol consumption (protective)
- Pollutants
- Selenium? Vitamin D?
- Infections (*Yersinia enterocolitica*)?
- Improved hygiene?

Endogenous
- Female sex
- Parity
- Aging
- Stress hormones
- Fetal microchimerism

Genetic
- Chromosome abnormalities
- Human leukocyte antigen types?
- Single-nucleotide polymorphisms?

Nutritional Factors

Excessand chronic iodine intake leads to autoimmune thyroiditis, because highly iodinated thyroglobulin (Tg) is more immunogenic. The HT patients are frequently iron deficient and treatment of anemic thyroid impaired women with iron improves the HT **[8]**. Vitamin D deficiency is related to HT, however, the direct mechanism for how low vitamin D leads to HT is not fully elicited. Vitamin Dstatus is lower in HT patients and inverse relationships of serum vitamin D with thyroid peroxidase/Tg antibodies. Supplementation of Vitamin D is required in patients with low vitamin D **[9]**. Seleniumis necessary for thyroid gland function. It has beneficial in thyroid antibody titers and mood in patients with HT. An excessive intake of selenium leads

to gastrointestinal distress and risk of type 2 diabetes and cancer. So, optimum level of the selenium is needed **[10]**. Vitamin B12 deficiency is seen patients with autoimmune thyroid disease. Vitamin B12 based diets is highly recommended for HT **[11]**.

Cruciferous vegetables (broccoli, cauliflower, cabbage, brussels sprouts etc.) drumstick leaves are rich source of glucosinates and isothyocyanates some of which are converted to progoitrin and goitrin. Goitrogens are compounds have adverse effect on thyroid gland and interfered with iodine on production of thyroxin hormones **[12]**. Soy is potential goitrogen and inhibited thyroxin synthesis and leads in goiter. The cooked crucifers and cruciferous is usually safe in HT. Coffee and fiber supplements decrease the absorption of thyroid medication which it is suggested 1-hour gap between the with thyroidmedication Flavonoids in fruits, vegetables and tea has potential cardiovascular benefit but high levels of the flavonoid reduced thyroid function **[13]**.

Zinc is involved in the production of thyroid hormones, and its deficiency leads to disturbances in antibody titers against thyroid antigens. Improvement of the nutritional status of this mineral in patients with HT restores normal thyroid function caused by its deficiency **[14]**. Magnesium has anti-inflammatory activity, including reducing the level of reactive C protein and the level of antibodies against thyroglobulin. A strong magnesium deficiency increases the risk of developing HT **[15]**.

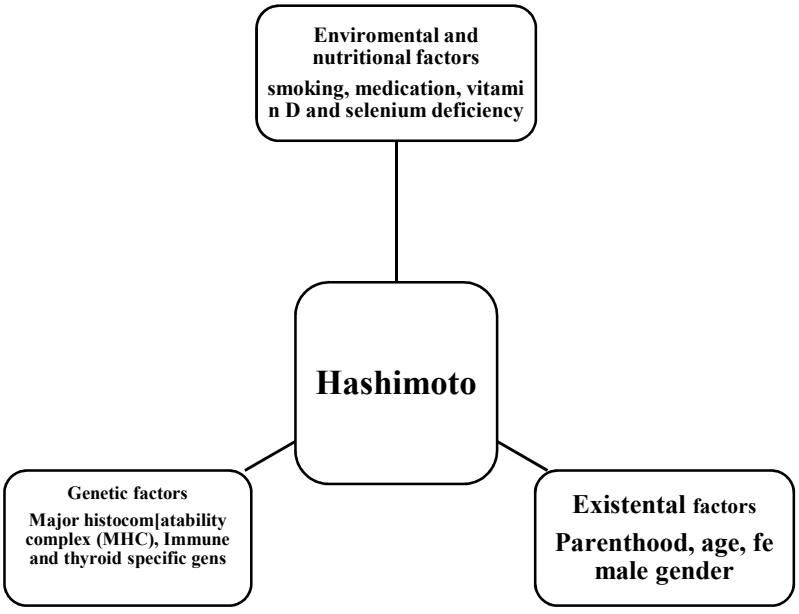

Figure 1

Genetic Factors

Genetic factors have crucial role in autoimmune thyroid disease. Under the influence of environmental factors, they incite the immune system and leads to over production of the antibodies to thyroid antigens **[2]**.The first group includes the HLA-DR, CD40, CTLA-4, and PTPN22 genes, while the second group includes the Thyroglobulin and stimulating thyrotropin (TSH) receptor genes. It is clear that additional genes contribute to the genetic susceptibility to Autoimmune thyroid diseases (AITD), as well as to the different phenotypes of AITD, disease severity, and, possibly, response to therapy. In addition, several environmental factors have been associated with the etiology of AITD, notably, dietary iodine, infections, smoking and certain medication **[16]**.

Physiological factors

Cardiovascular: Patients with hypothyroidism have higher cardiovascular diseases risk compared to whom with obesity. Low levels of thyroidhormones lead to increased blood pressure, blood lipid profile, homocysteine and inflammatory marker Creactive protein. Thyroid hormones play key role on cholesterol synthesis and degradation, receptors and cardiovascular diseases **[17]**. Hypothyroidism affects carbohydrate metabolism and body weight and usually happens in menopause which increases weight gain in women **[18]**.

Diabetes: based on the reports, autoimmunethyroid disease prevalence is 40% in type1 diabetes, 12.5% in type 2 diabetes and 6.6% in people without diabetes. Daily dose of levothyroxineis critical for thyroid hormone therapy. There is concern for doses of levothyroxine which younger patients can receive full dose but patients with heart disease should receive low doses **[19]**.

Pregnancy: During pregnancy, Hashimoto's disease-induced hypothyroidism occurs in 3-5out of every 1000 pregnancies. Miscarriage, premature birth, stillbirth and preeclampsia is usually seen in hypothyroidism. Untreated hypothyroidism during pregnancy has adverse effect on infant brain development and growth **[18]**. The selenium/selenoproteins can decrease thyroid peroxidase antibody titers, hypothyroidism, and postpartum thyroiditis **[20]**.

Existential factors

Mental health, has important role in development of the HT. Chronic stress affects body physiological status such as cardiovascular and immune system as well as antioxidant defense system **[21]**. Smoking, alcohol consumption, ionizing radiation and heavy metals increases free radicals and leads to thyroid dysfunction.

The thyroid gland affected by the oxidative stress **[21]**. There is relationship between HT and oxidative stress which **[22]** shows that the changes arising from thyroid aging concern the reduction of gene expression associated with mitochondrial and proteasome functions – important in autophagocytic processes and increased production of proteins associated with autoimmune processes. Oxidative stress is associated with the progression of HT while in patients with improved thyroid function, a simultaneous improvement of the antioxidant potential was observed. Examining the impact of diet on changes in the oxidation and reduction potential of the body, expressed in the total number of peroxides in plasma, a relationship between the consumption of vegetables and fruit in the diet and the amount of oxidative damage measured in the blood was established **[23]**.

Infections

Infections have been implicated in the pathogenesis of AITD. The best studied infection in this regard is that with *Yersinia enterocolitica*. There is a sound biologic rationale for a causal link between *Y. enterocolitica* infection and AITD. *Y. enterocolitica* has specific binding sites for TSH, which are recognized by TSH receptor antibodies isolated from patients with Graves disease. Conversely, immunization of mice with *Y. enterocolitica* leads to the induction of TSH receptor antibodies. YOP (*Y. enterocolitica* outer membrane protein) antibodies stain thyroid epithelial cells in immunochemistry. The *Y. enterocolitica* protein cross-reacting with TSH receptors has recently been identified: the YOP membrane porin F shared cross-immunogenicity with a leucine-rich domain of the TSH receptor **[24]**. The plausible theory then is that *Y. enterocolitica* ompF (outer membrane porin F) is involved in the production of TSH receptor antibodies and the pathogenesis of Graves disease through molecular mimicry. However, recent epidemiological studies do not support this theory. A nested case-control study in the Amsterdam AITD cohort looked into *de novo* occurrence of TPO-Ab in relation to *Y. enterocolitica* infection **[25].**

CONCLUSION

An underactive thyroid is known as hypothyroidism when the gland fails to produce enough thyroid hormone. Hashimoto's thyroiditis is an autoimmune disease that leads to hypothyroidism, the most common in the world wide. It is essential for physicians to test for antithyroid antibodies in every case of acute encephalopathy as a means of ruling out or further exploring a diagnosis of Hashimoto encephalopathy. While it remains an extremely rare cause, it is also one of the few treatable and easily

reversible causes of acute encephalopathy, making it much more important for the physician to recognize and treat.

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