Hashimoto Thyroiditis - A Comprehensive Review

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Abstract

Hashimoto thyroiditis (HT) is an inflammatory disorder that often results in hypothyroidism. It has several global implications affecting different regions worldwide. Risk factors for acquiring HT include diet, inheritance, sex, epigenetics, and comorbidities. HT is a complex autoimmune illness characterized by an attack on the thyroid gland by the immune system. At the cellular level, genetic predisposition, environmental triggers, and the loss of immunological tolerance to thyroid antigens all play significant roles in the disease's genesis and progression. There are several mechanisms by which HT may develop, but the typical progression is autoimmune in origin. Many patients do not initially present with symptoms, but later develop symptoms of hypothyroidism. These symptoms include constipation, fatigue, dry skin, weight gain, cold intolerance, decreased energy, memory loss, muscle cramps, hair loss, and irregular menses. Patients with HT usually present with a firm, nontender neck goiter on a physical exam. To distinguish HT from other thyroid pathologies, patient serum should be collected to check for thyroid-specific auto-antibodies against thyroglobulin, thyroid peroxidase, thyroid stimulating hormone. Imaging studies such as ultrasonography with computer-aided techniques using gray-scale features are also diagnostic tools in differentiating between a healthy thyroid and HT. While the most common intervention of HT is synthetic hormone administration with levothyroxine sodium (L-T4), other alternatives or additional treatments include glucocorticoid use, diet alterations, selenium supplementation, vitamin D supplementation, and in more extreme cases, thyroidectomy. While research continues discovering new interventions, each treatment plan is highly variable based on underlying causes and presentations. This comprehensive review hopes to provide an up-to-date compact analysis of literature pertinent to the epidemiology, etiology, risk factors, genetics, pathophysiology, classifications, clinical presentation, diagnosis, and treatments of HT.

1. Introduction

Hashimoto thyroiditis (HT) is an autoimmune disorder that leads to hypothyroidism. HT is named after Japanese physician Harkaru Hashimoto, and Dr. Hashimoto first reported the symptoms in 1912 in the journal Archiv für Klinische Chirurgie [1]. HT leads to chronic inflammation, increased thyroid size, and appearance of antibodies specific to thyroid gland. Globally, HT is the most prevalent autoimmune thyroid disease [2,3,4]. In regions in the world where iodine intake is sufficient, HT is the most common cause of hypothyroidism. Every year, 0.8 out of 1000 men and 3.5 out of 1000 women experience HT [5]. Another study revealed that the prevalence of HT ranged from 4.8–25.8% in women and 0.9–7.9% in men, confirming that HT is more common in women than men [6]. When comparing the concordance rate for monozygotic twins as compared with dizygotic twins, monozygotic had a high rate of 55% vs 0% of the dizygotic twins [7]. With respect to race, Caucasians have the highest rate of developing HT, with a total incidence rate of 5% [8]. Individuals with previously diagnosed autoimmune conditions have a greater risk of developing HT compared to those without any history [9]. A study conducted on the financial burden of hypothyroidism disorders...
estimated a yearly cost range of $460 to $2,555 per patient [10]. Additionally, an epidemiological study found that the prevalence of thyroid disorders increases with age [5].

2. Etiology and risk factors

Individuals with HT tend to develop autoantibodies towards the host's thyroid antigens [5]. Some examples of antigens include antibodies towards anti-thyroid peroxidase (AbTPO), anti-thyroglobulin (AbTg), and TSH receptor-blocking antibodies [5]. These autoantibodies contribute to the destruction of the thyroid gland parenchyma, which fails to produce appropriate amounts of thyroid hormone [5]. In 10-15% of individuals with HT, there is an absence of autoantibodies indicating another possible cause [5]. The cause of HT and the production of these self-antibodies is still unclear but several genetic factors, environmental factors, and epigenetic factors may play a role [11]. A study conducted by Brix et al showed when comparing monozygotic twins and dizygotic twins, monozygotic twins had a higher concordance rate of HT (50% vs 0%) and autoantibodies (80% vs 40%) [7,12]. When examining specific alleles, a case-control study showed having HLA-B*46:01 was associated with HT [13]. Ueda et al. also showed HLA-A* 02:07 and HLA-DRB4 were associated with HT [14]. Additionally, certain single nucleotide polymorphisms (SNPs) in genes associated with immune regulation have been associated with HT. SNPs in the genes of IL2R, CD14, PTPN22, CD40, and CTLA-4 have been linked to developing HT [15].

A known risk factor associated with HT is excess iodine intake. One study that used iodine as prophylaxis for iodine deficient patients showed that thyroid autoantibodies increased by a factor of two and HT rate increased by a factor of four after iodine consumption [16]. A meta-analysis showed that decreased selenium has also been associated with increased thyroid autoantibodies [17]. Additionally, radiation exposure has been implicated with HT and can be labeled a risk factor for HT [18]. Women have higher rates of HT, and a possible explanation is via an epigenetic mechanism of X inactivation in women, leading to more autoimmune thyroid diseases (AITD) [6,19].

3. Pathophysiology

At the molecular level, HT is caused by a complex combination of immune system dysregulation, hereditary factors, and environmental stimuli [20]. There are several mechanisms by which HT may develop, but the typical progression is autoimmune in origin, leading to infiltration by lymphocytes and development of fibrosis [5, 50]. Autoantibodies for TPO, Tg, and TSH receptors may be present; however, a small percentage of patients with HT may have none of these Abs, and some can have these Abs without developing HT [50]. Even so, it is accepted that a positive serum anti-TPO antibody concentration is correlated with the active phase of the disease [51].
In patients with HT and a positive serum anti-TPO antibody concentration, antibody-dependent cell-mediated cytotoxicity is an essential factor in apoptosis and the pathophysiology of HT, which have characteristics of both type IV and type II hypersensitivity reactions [50]. Initially, antigen-presenting cells (APC) (mostly dendritic cells and macrophages), infiltrate the thyroid gland in response to an environmental factor (dietary iodine, toxins, virus infection, etc.), which causes damage to thyrocytes and release of thyroid-specific proteins [9, 21, 22, 23]. These proteins serve as a source of self-antigenic peptides that are presented on the cell surface of APC [9]. In the draining lymph node, APCs interact with autoreactive T cells and B cells, which result in production of thyroid autoantibodies [9]. Then, antigen-producing B lymphocytes, cytotoxic T cells (CD8+ T cells) and macrophages infiltrate the thyroid tissue through clonal expansion [9]. As a result, they cause massive destruction and depletion of thyrocytes via antibody-dependent, cytokine-mediated and apoptotic mechanisms of cytotoxicity that lead to hypothyroidism and HT [9, 50]. This inflammatory process damages the thyroid tissue, reducing its ability to make and release thyroid hormones, which are essential for regulating metabolism in the body [24].

![Diagram of the immune response in HT](image)

**Figure 1**

Histologically, hypersensitivity is seen as a diffuse infiltration of the parenchyma by lymphocytes, especially plasma B cells, which can be visualized as secondary lymphoid follicles [50]. Severe thyroid atrophy is seen as dense and fibrous bands of collagen that remain within the thyroid capsule [50].

Other theories implicated immune complexes, containing thyroid directed antibodies, as culprits of thyroid destruction [5].

### 4. Classification:

HT can either affect the Tg produced by thyrocytes or the enzyme TPO [25]. These impaired proteins lead to diminished formation of T3 and T4 since iodide cannot be
oxidized to iodine [49]. The most prevalent autoantibody is IgG4, which can be used as an indicator for either IgG4 thyroiditis or non-IgG4 thyroiditis. [25]. Immunohistochemistry allows isolation of these antibodies in order to determine a distinguishing factor causing the disease.

Additionally, HT can be classified based on its morphological features; its grading depends on the infiltration of lymphoid cells. It ranges from the following: Grade 0, where there are no lymphoid cells present at all (healthy), Grade 1 (mild) follicular cells will be infiltrated by a few lymphocytes, Grade 2 (moderate) giant cell formation begins due to a moderate amount of lymphocyte infiltration, and Grade 3 (severe) extreme lymphocytic inflammation with development of germinal centers. This would be classified as a tertiary lymphoid organ with very few follicular cells left [26].

5. Clinical Presentation:

Many patients with HT initially do not present with any symptoms, even when the characteristic TPO antibodies are present in blood tests [5]. Additionally, patients may initially have spurts of hyperthyroid symptoms, as the initial destruction of thyroid cells may lead to the increased release of thyroid hormone into the bloodstream [5]. However, patients may later develop one or more symptoms of hypothyroidism when the antibody response causes enough destruction [5]. Early symptoms can include constipation, fatigue, dry skin, and weight gain [5]. Advanced symptoms may present as cold intolerance, decreased sweating, peripheral neuropathy, decreased energy, depression, dementia, memory loss, muscle cramps, joint pain, hair loss, apnea, and irregular and heavy menses [5]. In some cases, the inflammation causes the thyroid to become enlarged (goiter), which, although rare, may cause neck discomfort, difficulty swallowing, and voice hoarseness [5].

Common dermatologic findings include scaly and dry skin, especially on the extensor surfaces, palms, and soles [5]. Increased dermal mucopolysaccharides can cause water retention and, in turn, pale-colored skin [5]. Hair growth rate may slow down, and hair can be dry, coarse, dull, and brittle. In more severe cases, diffuse or partial alopecia may occur, as this is associated with thyroid autoimmunity [5, 27]. Additionally, severe hypothyroidism is associated with myxedema, which refers to edema of the skin and soft tissue [5, 28].

Cardiovascular symptoms are generally uncommon in most patients. However, a decrease in thyroid function can increase peripheral vascular resistance by as much as 50% to 60% and reduce cardiac output by as much as 30% to 50% [5]. Cardiac echocardiography has shown impaired relaxation in patients with subclinical hypothyroidism, eventually leading to low cardiac output with decreased heart rate and stroke volume as well as an increased risk for heart failure [29, 30]. Bradycardia may also occur due to a loss of chronotropic action of thyroid hormone directly on the sinoatrial (SA) cells [5]. Although rare, patients can also have an accumulation of fluid in the pleural and pericardial cavities [5].
Symptoms such as fatigue, exertional dyspnea, and exercise intolerance are likely due to limited pulmonary and cardiac reserve [5]. It has also been shown that hypothyroid rats show decreased endurance, which make muscle weakness and myopathy important clinical features as well [5].

6. Diagnosis

In the pathophysiology of HT, thyrocyte destruction by antibody/immune cell-mediated cytotoxicity leads to structural changes, including enlargement of the thyroid, parenchymal infiltration by inflammatory cells, fibroblastic proliferation, calcification, and vascular proliferation [31]. However, patients presenting with HT are usually asymptomatic, and symptoms of hypothyroidism are only present in 20% of patients [32]. Therefore, a detailed physical exam accompanied by imaging, ultrasound, and fine needle aspiration must be done to come up with an accurate differential diagnosis for HT.

During physical examination patients usually present with a firm, irregular, and non-tender neck goiter [33]. Neck pain and tenderness are usually rare with the erythrocyte sedimentation rate and white blood cell count also being normal in these patients [33]. The decisive indicator for HT is the presence of different thyroid-specific autoantibodies in serum, such as antibodies against Tg, antibodies against TPO (also called thyroid microsomal antigen), and antibodies against thyroid stimulating hormone [34]. Antithyroid microsomal antibodies in titers greater than 1:6,400 or AbTPO antibodies above 200 IU per mL are strongly suggestive of HT [34].

Studies have also shown ultrasonography to be a useful tool for confirming a diagnosis of HT. In a study done by Mazziotti and colleagues, by using ultrasonography they evaluated 89 patients vs 40 healthy controls, and found that thyroid echogenicity evaluated by gray-scale quantitative analysis was lower in patients with the disease and that thyroid hypoechogenicity was associated with the occurrence of hypothyroidism in the patients [35]. In 2013, Acharya and colleagues devised a computer-aided technique using gray-scale features and classifiers, applied it to ultrasonography, and were able to find differentiation between Hashimoto’s thyroiditis and healthy thyroids with an accuracy of 80%, sensitivity of 76%, specificity of 84%, and positive predictive value of 83.3% [36].

7. Treatment

Hormone replacement therapy is a common approach for the management of hypothyroidism due to HT. In most cases, the synthetic hormone administered is levothyroxine sodium (L-T4) [37]. It is typically administered orally with the recommended dosage dependent on the patient’s body weight, ranging from 1.6 to 1.8 micrograms per kilogram [37]. The duration of this treatment is generally lifelong because the underlying cause often cannot be cured. However, in certain selected cases, L-T4 treatment may not be necessary, and clinical observation alone may be
sufficient. These cases typically involve individuals with subclinical hypothyroidism or mild thyroid dysfunction [37].

Some individuals receiving L-T4 treatment may experience persistent symptoms and reduced quality of life, despite achieving normal thyroid hormone levels. These symptoms include chronic fatigue, weakness, nervousness, irritability, mood swings, and impaired sexual activity [38]. One factor that has been investigated is the presence of high levels of circulating AbTPO, particularly in women [38]. Studies have shown that women with elevated AbTPO levels may be more prone to experiencing persistent symptoms despite being euthyroid with L-T4 treatment [39]. In addition to AbTPO, other factors may contribute to persistent hypothyroid symptoms. Some researchers have suggested that the traditional treatment approach with L-T4 alone may not fully address all aspects of thyroid hormone regulation in the body [39]. This has led to an exploration of alternative treatment strategies, such as combination therapy with both L-T4 and T3 [38, 39].

The use of glucocorticoids in the context of HT has been a topic of discussion and research. Some studies suggest that the acute use of high-dose glucocorticoids can have a positive effect on thyroid function by reducing inflammation and suppressing the auto-immune response [40]. However, the long-term use of high-dose glucocorticoids is generally considered to carry significant side effects, which may outweigh the potential benefits in most cases [40]. There is some evidence that suggests that the use of glucocorticoids, such as prednisolone, may have longer-term benefits in a subgroup with IgG4-related disease [41]. However, further research is needed to fully understand the efficacy and safety of this particular context.

The role of a specific diet in the management of HT has also been under investigation. While diet alone cannot cure the underlying condition, certain dietary factors, including iodine intake, are under consideration [40]. Excessive iodine intake has been postulated to potentially contribute to the exacerbation of thyroid autoimmunity because it is suggested that high levels of iodine can increase the immunogenicity of Tg [40]. On the other hand, appropriate iodine supplementation is important during pregnancy with a recommended intake of around 250 micrograms per day [40].

There are potential benefits of selenium supplementation in individuals with HT [42]. It has been suggested that selenium supplementation, particularly in individuals with selenium deficiency, may have a protective effect on the thyroid gland [11]. A systematic review found that selenium supplementation was associated with a reduction in serum AbTPO and AbTg antibodies levels. However, the study did not find a significant correlation between baseline selenium levels and the decrease in AbTPO levels [42]. Another meta-analysis evaluated the efficacy of selenium supplementation on various outcomes, including TSH levels, health-related quality of life, and thyroid ultrasound. This review did not find any significant effects of selenium supplementation on these outcomes in individuals not receiving levothyroxine replacement therapy [43,44]. The evaluation of clinically relevant outcomes in individuals receiving levothyroxine replacement therapy was sporadic and limited [43, 44]. Studies also
suggest that vitamin D deficiency may play a role in the development and progression of HT [11]. Given the low cost and minimal side effects associated with oral vitamin D supplementation, some healthcare professionals suggest that screening for vitamin D deficiency and subsequent supplementation may be beneficial for patients with HT [11, 45].

The use of surgery in the management of HT is generally limited and reserved for specific situations such as the compressions of nearby structures or malignancy [46]. It's important to note that thyroidectomy in HT patients carries a higher risk of complications compared to surgery performed for other thyroid disorders [47]. The chronic inflammation and fibrosis associated with HT can make the surgical procedure technically challenging and increase the likelihood of postoperative complications [47]. Thyroid gland transplantation has been proposed as a potential method to correct hypothyroidism in HT. However, further studies are needed to validate the efficacy and safety of this procedure [48].

8. Linked Conditions

Hashimoto's Thyroiditis, being an autoimmune disorder, is often associated with various linked conditions due to the shared underlying immune dysfunction [52]. Individuals with Hashimoto's thyroiditis are more likely to acquire other autoimmune conditions, such as rheumatoid arthritis, type 1 diabetes, systemic lupus erythematosus, or celiac disease [52]. This demonstrates the linked nature of autoimmune disorders and the potential for a person's immune system to target various organs or tissues. Individuals with Hashimoto's Thyroiditis also have a higher prevalence of thyroid-related diseases [52]. For example, some people may develop thyroid nodules, which are abnormal growths in the thyroid gland [52]. While the majority of nodules are benign, it is critical to monitor them for any signs of malignancies.

Hashimoto's Thyroiditis may potentially have an impact on fertility and pregnancy [54]. Women with the condition may experience menstrual irregularities, and if left untreated, it may impact fertility [54]. Miscarriage, preterm birth, and gestational diabetes are all more likely throughout pregnancy [54]. Thyroid hormone levels must be properly managed during pregnancy to provide the best outcomes for both the mother and the baby.

Moreover, there is some evidence that Hashimoto's Thyroiditis is associated with an increased risk of certain cardiovascular problems [53]. Several studies have revealed a link between this thyroid issue and disorders such as hypertension, dyslipidemia (abnormal lipid levels), and atherosclerosis [53]. More research, however, is required to determine the precise nature of this link.

Individuals with Hashimoto's Thyroiditis must be aware of these related illnesses and work closely with their healthcare professionals to ensure thorough management. Regular monitoring, suitable therapy, and lifestyle changes can all help to reduce the
effects of Hashimoto's and its associated diseases, increasing overall health and well-being.

9. Conclusion

This comprehensive review brings forth a concise analysis of the autoimmune thyroid disorder, Hashimoto thyroiditis. This paper provides the most current information on the epidemiology, etiology, pathophysiology, risk factors, classifications, clinical presentation, diagnosis, and treatment of Hashimoto thyroiditis. We desire that this paper may service clinicians, scientists, or anyone interested in furthering their knowledge of this disorder.

Abbreviations:

Hashimoto thyroiditis (HT)
Thyroglobulin (Tg)
Anti-thyroglobulin (AbTg)
Thyroid peroxidase (TPO)
Anti-thyroid peroxidase (AbTPO)

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