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Etiology of Hashimoto's Thyroiditis: A Literature Review of Genetic, Environmental, Epigenetic, and Immunologic Factors

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ABSTRACT

Hashimoto's thyroiditis (HT) is the most prevalent autoimmune thyroid disorder, affecting ~1–2% of adults, with a 7–10-fold higher incidence in women. The disease involves chronic inflammation, anti-thyroid antibody production, and progressive thyroid failure, particularly in iodine-replete regions. This review aims to consolidate current evidence on HT's etiology, encompassing genetic factors, environmental exposures, epigenetic regulation, and immunologic mechanisms, as well as highlight future research and intervention directions.The review was based on research of articles published in the PubMed database using the following keywords: Hashimoto's thyroiditis, autoimmune thyroid disease, thyroid autoimmunity, genetic susceptibility, HLA, CTLA-4, PTPN22, FOXP3, environmental triggers, iodine, Epstein-Barr virus, gut microbiota, vitamin D, oxidative stress, immunopathogenesis, T regulatory cells, Th1, Th17, thyroid peroxidase, thyroglobulin, and apoptosis. The analysis integrates molecular and cellular mechanisms, recent clinical findings, and immunological models to provide a comprehensive and up-to-date understanding of the disease.Recent studies confirm that HT arises from a multifactorial combination of genetic, environmental, and immunological factors. The growing body of evidence from immunogenetic and molecular studies supports a model in which impaired immune regulation, triggered by exogenous factors, leads to chronic lymphocytic infiltration of the thyroid gland. Understanding these mechanisms not only enhances diagnostic accuracy but also offers insight into future therapeutic interventions, including vitamin D supplementation, microbiota modulation, and targeted immunotherapies. Continued research in immunogenomics, environmental epidemiology, and cellular immunology is crucial for identifying individuals at risk and developing strategies to prevent, delay, or modify the course of the disease.

KEYWORDS: Hashimoto's thyroiditis, autoimmune thyroid disease, genetic susceptibility, environmental triggers, oxidative stress.

MATERIALS AND METHODS

The review was based on research of articles published in the PubMed database using the following keywords: Hashimoto's thyroiditis, autoimmune thyroid disease, thyroid autoimmunity, genetic susceptibility, HLA,

CTLA-4, PTPN22, FOXP3, environmental triggers, iodine, Epstein-Barr virus, gut microbiota, vitamin D, oxidative stress, immunopathogenesis, T regulatory cells, Th1, Th17, thyroid peroxidase, thyroglobulin, and apoptosis. Only peer-reviewed, full-text scientific articles published in English were considered. The selection included original research articles, systematic reviews, meta-analyses, and expert consensus statements. Emphasis was placed on studies that investigated the immunological, genetic, and environmental factors contributing to the pathogenesis of Hashimoto's thyroiditis. The analysis integrates molecular and cellular mechanisms, recent clinical findings, and immunological models to provide a comprehensive and up-to-date understanding of the disease.

INTRODUCTION

Hashimoto's thyroiditis (HT) is a chronic autoimmune condition predominantly affecting women (F:M ~7–10:1) [1]. Its etiology involves strong genetic predispositions—including polymorphisms in HLA-DR, CTLA-4, PTPN22, CD40, FOXE1, IL-2R, Tg, and TSHR—which have been identified through genome-wide and candidate gene studies [2–7]. Environmental contributors, such as excess iodine intake [8], selenium [9] and vitamin D deficiencies [10], viral infections (e.g., EBV, HCV, SARS-CoV-2) [11,12], medications (e.g., interferon-α, amiodarone) [13], toxins (like BPA, PCBs) [14], psychological stress [15], and fetal microchimerism [16] also influence disease onset. Epigenetic modifications, including DNA methylation, histone acetylation, and non-coding RNAs, have been shown to regulate key immune genes and influence immune tolerance [17–19]. These gene-environment interactions promote Th1/Th17 activation, autoantibody production (anti-TPO, anti-Tg), and thyroid cell destruction [20–23]. This review synthesizes evidence from EBM studies. It highlights gaps in our understanding of the gut microbiome [24], epigenetic regulation, and personalized immunotherapy approaches. Future research should focus on randomized trials of selenium and vitamin D supplementation as preventive interventions [9,10], longitudinal multi-omic studies [25], and the development of genotype-based predictive models for early disease detection and targeted prevention [26,27].

1. Genetic Susceptibility

HT is associated with specific HLA alleles (DR3, DR5, DQ7) that influence antigen presentation [28–30]. Polymorphisms in CTLA-4, PTPN22, and CD40 are also implicated in disease susceptibility [31–33]. Variations in thyroid-specific genes—thyroglobulin (Tg), TSHR, and NIS—exert milder yet significant effects [34]. Individuals with Turner and Down syndromes exhibit higher HT prevalence (19–30%) compared to general rates, supporting genetic contribution [35–37]. Twin studies reveal ~55% concordance in monozygotic pairs and ~80% concordance of thyroid antibodies, with heritability estimates around 75–80% [1,39].

1.1. Familial Aggregation and Twin Studies

The heritability of autoimmune thyroid disease (AITD), including HT, is among the highest for autoimmune disorders. Familial clustering is common, with first-degree relatives of patients showing a 5–15 % increased risk of developing thyroid autoimmunity themselves [40]. Twin studies provide compelling evidence: monozygotic twins show a concordance rate of approximately 55 %, whereas dizygotic twins exhibit only about 3–9 % concordance [41,42]. This stark contrast underscores the significance of genetic factors, though

incomplete concordance among identical twins also highlights the importance of environmental and epigenetic modifiers.

1.2. Major Histocompatibility Complex (MHC) / HLA Class II Genes

The most strongly associated genetic region with HT lies within the major histocompatibility complex (MHC) on chromosome 6p21.3, particularly HLA class II alleles such as HLA-DR3, HLA-DR5, HLA-DR4, and HLA-DQ7 [43,44]. These genes encode molecules that present antigenic peptides to CD4+ T cells, thereby orchestrating immune responses. Specific alleles show ethnic variation in frequency; for example, HLA-DR5 is more frequently associated with HT in Caucasian populations, whereas HLA-DR3 predominates in Japanese and Mediterranean cohorts [44,45].

1.3. CTLA-4 (Cytotoxic T-Lymphocyte–Associated Antigen 4)

CTLA-4, located on chromosome 2q33, encodes a negative regulator of T-cell activation. The +49A/G (rs231775) polymorphism is significantly associated with increased susceptibility to Hashimoto's thyroiditis (HT) [46]. This SNP alters CTLA-4 function or expression, reducing the threshold for T-cell activation and promoting autoimmunity. Multiple meta-analyses, including the pivotal one by Tian et al., have confirmed a robust association across diverse ethnic groups, particularly among Asians [47]. Furthermore, CTLA-4 polymorphisms correlate with more severe HT phenotypes, such as elevated anti-TPO antibody levels and deeper hypothyroidism [48].

1.4. PTPN22 (Protein Tyrosine Phosphatase Nonreceptor Type 22)

PTPN22 encodes the lymphoid-specific phosphatase LYP, a key regulator that dampens T-cell receptor signaling. The R620W (rs2476601) polymorphism has been linked to heightened risk of HT as well as other autoimmune diseases like type 1 diabetes and rheumatoid arthritis [49]. This gain-of-function variant paradoxically impairs deletion of autoreactive T-cells in the thymus, facilitating autoimmune development [50]. Meta-analyses confirm that R620W is significantly associated with HT in Caucasian populations [51].

1.5. FOXP3 and Regulatory T Cell Genes

FOXP3, a transcription factor essential for regulatory T cell development and function, has been implicated in the pathogenesis of HT. While FOXP3 repressor mutations cause IPEX syndrome, promoter polymorphisms (e.g., –3279 A/C, rs2232368) are linked with subtle reductions in Treg efficiency and increased risk of HT, particularly noted in certain ethnic populations [52,53]. Skewed X-chromosome inactivation in females may decrease FOXP3 expression, providing insight into the strong female bias observed in HT [54].

1.6. Thyroid-Specific Genes

Thyroid autoantigens such as thyroglobulin (Tg) and the thyroid-stimulating hormone receptor (TSHR) display genetic variability that influences disease susceptibility. Polymorphisms in the Tg gene (e.g., promoter rs180195, intronic Tgms2) are associated with HT, potentially by enhancing antigenicity or altering peptide

presentation [55,56]. TSHR polymorphisms, while more robustly linked to Graves' disease, also contribute to HT risk through shared autoimmune regulatory mechanisms [57].

1.7. CD40 and Other Immune-Modulating Genes in Hashimoto's Thyroiditis

CD40 is a costimulatory molecule expressed on antigen-presenting cells, playing a crucial role in T cell activation. The rs1883832 polymorphism in the CD40 gene is strongly associated with Graves' disease, but meta-analyses demonstrate no significant link between this variant and HT susceptibility [58]. IL2RA encodes the IL-2 receptor α-chain, essential for Treg proliferation. Although rs7093069 has been studied, the evidence shows no definitive association with HT [59]. STAT4 is required for Th17 cell differentiation. A meta-analysis of 5 studies (n=1707 patients) confirmed a significant association between rs7574865 and AITD, including HT [60]. IL-17A and IL-17F cytokines are elevated in HT patients; the IL-17F rs763780 polymorphism is also associated with autoimmune thyroiditis [61]. TGFA and TGF-β1, involved in immune regulation and tissue remodeling, have demonstrated molecular involvement in HT; however, genetic data—such as TGF-β1 Arg25Pro (c.915G>C)—yield inconclusive evidence [62].

1.8. Polygenic Risk Models and GWAS Findings

Recent genome-wide association studies (GWAS) have confirmed the polygenic nature of Hashimoto's thyroiditis (HT). Multiple loci, each contributing modestly, collectively determine susceptibility. Polygenic risk scores (PRS) are being developed to predict lifetime HT risk based on cumulative genetic load. Notably, many HT-associated variants overlap with those implicated in other autoimmune diseases—such as type 1 diabetes, celiac disease, and systemic lupus erythematosus—suggesting shared pathogenic pathways [63].

1.9. Chromosomal Syndromes and Increased Risk

Patients with chromosomal anomalies—Turner syndrome (XO) and Down syndrome (trisomy 21)—exhibit increased HT prevalence (15–30% vs. 2–5% in the general population) [64,65,66]. In Turner syndrome, haploinsufficiency of X-linked immune genes may impair Treg function and central tolerance. In Down syndrome, overexpression of chromosome 21 genes likely skews immune development and promotes pro-inflammatory responses. These syndromes highlight the importance of chromosomal context and gene dosage in immune regulation.

1.10. Gene-Gene and Gene-Environment Interactions in Hashimoto's Thyroiditis

The development of Hashimoto's thyroiditis (HT) requires genetic predisposition; however, genetics alone are insufficient to fully explain disease onset. Increasing evidence highlights the importance of gene-gene interactions (epistasis) and gene-environment interactions in modulating disease risk and clinical expression [67,68].

Gene-Gene Interactions

Polymorphisms in several immune-regulatory genes such as HLA-DR3, CTLA-4, and PTPN22 have been individually associated with HT susceptibility [69–71]. Studies demonstrate that the coexistence of risk alleles in these genes can synergistically increase the likelihood of autoimmune thyroid disease. For example,

combined presence of high-risk variants in HLA-DR and PTPN22 genes amplifies aberrant T cell activation and breakdown of immune tolerance, facilitating autoantibody production and thyroid damage [72,73]. Such epistatic effects underscore the complex polygenic architecture of HT.

Gene-Environment Interactions

Environmental factors such as iodine intake, viral infections (e.g., Epstein-Barr virus), stress, and exposure to endocrine-disrupting chemicals modulate gene expression and immune responses [74,75]. Notably, individuals carrying susceptible alleles in HLA-DR3, CTLA-4, and PTPN22 genes appear more vulnerable to iodine-induced thyroid autoimmunity, suggesting an interaction where excess iodine acts as a trigger in genetically predisposed hosts [76,77]. Furthermore, epigenetic mechanisms including DNA methylation, histone modifications, and non-coding RNAs dynamically regulate gene expression in response to environmental stimuli [78,79]. These modifications can enhance or suppress expression of immune-related genes, thereby influencing disease penetrance and severity [80]. For instance, aberrant methylation patterns in immune checkpoint genes may exacerbate loss of self-tolerance in HT [81]. This intricate network of gene-gene and gene-environment interactions explains the variable clinical presentation and incomplete penetrance observed among genetically predisposed individuals [82].

Conclusion of Section

The genetic architecture of Hashimoto's thyroiditis is multifaceted, involving both immune-regulatory and thyroid-specific genes. Strong evidence supports critical roles for HLA alleles, CTLA-4, PTPN22, and other immune-modulating loci, with interactions among these genes amplifying disease risk. Genetic susceptibility provides a necessary but not sufficient foundation for autoimmunity; environmental exposures and epigenetic regulation critically modulate disease expression. Future research should focus on refining polygenic risk scores, identifying protective alleles, and elucidating gene-environment interplay to facilitate personalized prediction, prevention, and therapeutic strategies in HT.

2. Environmental Triggers

While genetic predisposition sets the foundation for Hashimoto's thyroiditis (HT), environmental triggers play a crucial role in disease onset and progression. The incomplete concordance between monozygotic twins, the increasing prevalence of HT in industrialized societies, and the geographical clustering of autoimmune thyroid diseases (AITDs) support the contribution of environmental factors. These triggers interact with susceptible genetic backgrounds to alter immune tolerance and promote thyroid-specific autoimmunity [83,84].

2.1. Excessive Iodine Intake

Iodine is essential for thyroid hormone synthesis, but excessive intake is a well-recognized trigger for AITDs. It enhances the immunogenicity of thyroglobulin (Tg) and increases expression of thyroid autoantigens such as Tg and thyroid peroxidase (TPO) [85,86]. Population studies, including Chinese cohorts in regions with high urinary iodine concentrations (UIC $\geq$300 μg/L), report elevated anti-TPO titers and increased HT prevalence [86]. Mechanistically, iodine excess induces oxidative stress in thyrocytes, promoting apoptosis, autoantigen release, and subsequent immune activation in genetically predisposed individuals [85,87]. The risk appears

dose-dependent, with moderate supplementation being largely safe, while abrupt high intake (e.g., from contrast agents or supplements) may precipitate thyroiditis [88].

2.2. Infections and Molecular Mimicry

Infectious agents are implicated in AITD pathogenesis via mechanisms including molecular mimicry, bystander activation, and epitope spreading. Key pathogens include: Epstein–Barr Virus (EBV): HT patients consistently exhibit higher EBV viral loads and antibody titers compared to controls. EBV latent proteins may mimic thyroid antigens or infect thyroid tissue directly, triggering immune activation [89,90]. Hepatitis C Virus (HCV): Particularly in the context of interferon-α therapy, HCV infection unmasked HT in susceptible individuals, potentially through similar molecular mimicry mechanisms [91]. Yersinia enterocolitica: Certain Yersinia outer proteins (YOPs) share structural homology with human TSH receptor and thyroid autoantigens. Elevated anti-YOP antibodies have been detected in ~28% of HT patients versus ~2% of controls, supporting a mimicry hypothesis [92,93]. Though causality remains uncertain, these findings suggest a potential contributory role in genetically predisposed hosts. Other pathogens (e.g., rubella virus, Coxsackie B) have been proposed but lack strong supporting epidemiologic data.

2.3. Environmental Toxins and Pollutants

Exposure to environmental chemicals—many acting as endocrine disruptors—has been linked to thyroid dysfunction and autoimmunity. These include Bisphenol A (BPA), phthalates, polychlorinated biphenyls (PCBs), perchlorate, and heavy metals (e.g., mercury, cadmium) [94,95]. BPA, commonly found in plastics, may bind estrogen receptors, interfere with thyroid hormone synthesis/metabolism, and modulate immune responses. A cross-sectional study in women of reproductive age reported no significant direct association between urinary BPA and AITD; however, some mechanistic evidence suggests impacts on immune regulation and thyroid function via epigenetic pathways [94,96,97]. PCBs and dioxins have been shown in animal models to induce thyroiditis-like pathology, accumulating in the gland, causing chronic oxidative damage and autoantigen exposure [95]. Occupational exposure to solvents and pesticides is associated with a higher incidence of AITD, particularly in agricultural settings [95]. These pollutants may damage thyroid follicular cells, impair immune homeostasis, and modulate gene expression through epigenetic mechanisms [94–96].

2.4. Smoking and Alcohol

Smoking: Paradoxically, although smoking increases Graves' disease risk, multiple studies report that smoking is protective against HT. A Korean population study showed smokers had lower TPO-Ig titers and reduced HT prevalence [97]. Nicotine’s immunomodulatory effects—like pro-inflammatory cytokine suppression—may dampen HT pathogenesis [98]. Alcohol: Moderate alcohol consumption correlates with reduced HT risk. Proposed mechanisms include suppression of T cell activation, reduced antigen presentation, and promotion of regulatory immune pathways [99,100,101]. However, due to risks of alcohol use, these findings are not supportive of alcohol as therapy.

2.5 Stress and Psychoneuroimmunology

Chronic psychological stress modulates immune function through activation of the hypothalamic–pituitary–adrenal (HPA) axis, leading to sustained elevation of cortisol and glucocorticoids. These hormones suppress Th1-mediated cellular immunity (e.g., IL-2, IFN-γ) and favor Th2-skewed humoral responses, mechanisms implicated in the pathogenesis of autoimmune thyroiditis [101,102]. Animal studies demonstrate that chronic stress disrupts thyroid hormone homeostasis—reducing T_3 levels and dampening humoral immunity—with effects that are reversible upon thyroid hormone replacement [103]. Clinically, psychosocial stress has been associated with increased risk of postpartum thyroiditis and is hypothesized to contribute to Hashimoto's thyroiditis through similar immunomodulatory pathways [104,105].

2.6 Vitamin D Deficiency

Vitamin D is recognized as a key immunomodulator that enhances regulatory T cell (Treg) differentiation while suppressing Th1 and Th17-mediated inflammatory responses. Observational research, including a meta-analysis of 26 case–control studies encompassing 2,695 patients, consistently shows significantly lower serum 25-hydroxyvitamin D (25(OH)D) levels in individuals with Hashimoto's thyroiditis (HT) compared to healthy controls (standardized mean difference –0.62; OR 3.21 for vitamin D deficiency) [106]. Mechanistically, vitamin D engages its receptor (VDR) on antigen-presenting cells and T lymphocytes, resulting in reduced production of pro-inflammatory cytokines such as IL-2, IL-17, and TNF-α, promotion of anti-inflammatory cytokines (IL-10), inhibition of dendritic cell maturation, induction of tolerogenic Treg cells, and suppression of B-cell differentiation into autoantibody-secreting plasma cells [107,108]. In HT patients, VDR polymorphisms—such as FokI, BsmI, ApaI, and TaqI—have been associated with increased disease susceptibility. One case–control study showed that serum 25(OH)D levels were significantly lower in HT subjects (median 16.2 ng/mL vs 37.4 ng/mL in controls), and those with vitamin D deficiency had significantly higher TPO antibody titres, although no differences in VDR BsmI/ ApaI/ TaqI genotypes were observed [107]. Although supplementation trials remain limited, preliminary randomized and interventional studies have demonstrated that cholecalciferol supplementation (e.g., 50,000 IU weekly) can reduce anti-thyroid antibody titres and restore Treg/Th17 balance in HT patients [106]. These findings support the recommendation of vitamin D supplementation in HT cases with confirmed deficiency [108].

2.7 Gut Microbiota and the Microbiome–Thyroid Axis

Emerging evidence underscores an influential "gut–thyroid axis" in autoimmune thyroid disorders. A 2021 meta-analysis including 196 patients with autoimmune thyroid disease (AITD), of whom some had Hashimoto's thyroiditis (HT), revealed significant gut dysbiosis: reduced alpha diversity, decreased abundance of Lactobacillus and Bifidobacterium, and increased levels of pathobionts such as Bacteroides fragilis and phyla Proteobacteria [109]. Independent cross-sectional analyses using 16S rRNA sequencing corroborate these findings, demonstrating depletion of commensal genera (e.g., Fecalibacterium, Bacteroides, Prevotella) and enrichment of inflammatory genera (e.g., Blautia, Roseburia, Ruminococcus_torques, Enterobacteriaceae) alongside elevated markers of intestinal permeability, such as zonulin, in HT patients [110,111]. These alterations are mechanistically linked to systemic inflammation via increased translocation of microbial antigens ("leaky gut"), which may initiate or exacerbate thyroid autoimmunity [111,112]. While interventional trials

remain scarce, strategies including probiotics and dietary modulation targeting microbiota composition show preliminary therapeutic potential [110,112].

2.8 Radiation Exposure

Exposure to ionizing radiation—whether therapeutic, diagnostic, or environmental—has been consistently implicated in heightened risk for autoimmune thyroid disease. Following the Chernobyl nuclear disaster, a case–control study of 143 children in contaminated regions reported a fourfold increase in anti-TPO and anti-Tg antibodies compared to unexposed peers (19% vs. 5%) [113]. These findings support dose-dependent relationships between radioiodine exposure and thyroid autoimmunity, whereby radiation-induced thyroid damage leads to antigen release and immune activation in genetically susceptible individuals.

2.9 Pregnancy and Postpartum Period

Pregnancy induces a physiological immunotolerant state to protect the semi-allogeneic fetus, characterized by shifts in Th1/Th2 cytokine balance and expansion of regulatory T cells. However, the postpartum period is marked by immune rebound, which increases susceptibility to autoimmune diseases, including postpartum thyroiditis (PPT), a variant of Hashimoto's thyroiditis [114]. Mechanistically, several phenomena contribute to postpartum thyroid dysfunction: Th1/Th2 cytokine balance shift: During pregnancy, a Th2-skewed environment prevails, which reverses postpartum and promotes Th1-mediated inflammatory responses implicated in thyroid autoimmunity [114]. Fetal microchimerism: Persistence of fetal cells in maternal blood and thyroid tissue may trigger graft-versus-host-like immune reactions following the loss of pregnancy-induced immunosuppression [115,116]. Epigenetic reprogramming of immune cells: Postpartum immune rebound may influence immune cell epigenetics, altering gene expression patterns in T and B lymphocytes that predispose to autoimmunity, although specific epigenetic mechanisms in PPT remain under investigation [117]. Epidemiological data indicate that approximately 4–8% of unselected women develop PPT within 12 months post-delivery, with higher prevalence (up to ~20%) in those positive for thyroid autoantibodies or with a family history [114,118]. PPT typically follows a biphasic course (thyrotoxicosis then hypothyroidism) and about 25–30% of cases progress to permanent hypothyroidism within 5–10 years, especially in antibody-positive women [114,118].

Conclusion of Section:

Environmental triggers play a critical role in unmasking or accelerating Hashimoto's thyroiditis in genetically predisposed individuals. Excessive iodine intake, infections, environmental toxins, stress, vitamin D deficiency, and changes in the gut microbiome each contribute to immune dysregulation and thyroid-specific autoimmunity. These factors rarely act in isolation but interact synergistically with genetic and epigenetic mechanisms. Understanding these triggers provides potential avenues for prevention, early diagnosis, and lifestyle interventions in HT management.

3. Gene–Environment Interactions & Epigenetics

Emerging evidence implicates epigenetic dysregulation as a pivotal mediator between environmental exposures and genetic predisposition in autoimmune thyroid disease (AITD). Key targets include immune-regulatory genes such as CTLA-4 and FOXP3, where alterations in DNA methylation and histone modification influence

T-cell differentiation and self-tolerance [119]. MicroRNAs, notably miR-146a, have been shown to modulate immune responses in HT: lower miR-146a expression correlates with heightened pro-inflammatory cytokine production in peripheral blood mononuclear cells [119,120]. Moreover, patterns of histone acetylation in promoters of regulatory loci further contribute to aberrant gene activation in AITD [119]. A striking epigenetic mechanism that may underlie the pronounced female bias in HT is skewed X-chromosome inactivation (XCI). Multiple case-control studies on adult and pediatric HT cohorts have reported significantly increased prevalence of skewed XCI (>80% skewing) in patients versus controls, with odds ratios between 4 and 9 [121,122]. Skewing may lead to mosaic expression of X-linked self-antigens (e.g., FOXP3, CD40L, TLR7), which escape central tolerance, thereby triggering autoreactive T-cell responses in genetically susceptible females [121]. Enhanced XCI skewing in childhood-onset AITD suggests its contribution from early life [122]. Environmental factors such as infection, ionizing radiation, and iodine excess may further induce epigenetic changes, including locus-specific demethylation or histone acetylation, priming immune-regulatory genes for aberrant expression [119,120,123]. In this context, gene–environment interactions operate through epigenomic modulation, establishing a "two-hit" model in which genetic susceptibility and epigenetic alterations coalesce to break immune tolerance [119,123].

4. Immunopathogenesis

Hashimoto's thyroiditis (HT) is characterized by a complex immune-mediated destruction of the thyroid gland, resulting from a breakdown in self-tolerance to thyroid antigens. Both innate and adaptive immunity contribute, driven by genetic predisposition, environmental triggers, and regulatory failure.

4.1 Loss of Immune Tolerance

Central to HT pathogenesis is the failure of tolerance mechanisms to thyroid-specific proteins such as thyroglobulin (Tg) and thyroid peroxidase (TPO). Normally, autoreactive T cells are excluded via thymic negative selection and peripheral regulatory mechanisms including regulatory T cells (Tregs), anergy, and immune checkpoints (e.g., CTLA-4). Polymorphisms in genes like PTPN22, CTLA-4, and FOXP3 compromise both central and peripheral tolerance, allowing autoreactive T cells to persist and invade the thyroid gland [124,125].

4.2 Role of Antigen-Presenting Cells and Thyroid Follicular Cells

In HT, dendritic cells and macrophages present TPO and Tg peptides on HLA class II molecules, activating naïve CD4+ T helper cells. Thyroid follicular cells also aberrantly express MHC class II in response to IFN-γ, allowing them to present autoantigens and amplify local inflammation [126,127].

4.3 T Helper Cell Subsets and Cytokine Profiles

HT exhibits a predominance of Th1-type responses, with IFN-γ, IL-2 and TNF-α promoting macrophage and cytotoxic CD8+ T-cell–mediated follicular damage. Th17 cells, producing IL-17, are increasingly recognized in HT; their levels correlate with fibrosis and disease severity [128]. Autoreactive Th1/Th17 cells are activated by thyroid antigen presentation, leading to complement activation, thyrocyte apoptosis, and tissue remodeling [126,128]. Treg dysfunction—quantitative and qualitative—further disrupts immune homeostasis. Patients

display decreased CD4+CD25highFOXP3+ Tregs and impaired suppressive activity, allowing unchecked effector T-cell responses [129]. The imbalance between Treg and Th17 frequencies correlates with autoantibody levels and disease activity [129].

4.4 B Cells and Autoantibodies

B lymphocytes play key roles in Hashimoto's thyroiditis (HT) pathogenesis through antigen presentation, cytokine secretion, and production of thyroid autoantibodies. The predominant autoantibodies, anti–thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg), are present in over 90% of HT patients and serve as essential diagnostic biomarkers [130]. Although the direct pathogenic contribution of these antibodies is debated, anti–TPO antibodies mediate both complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) against thyrocytes [131,132]. B cells also secrete pro-inflammatory cytokines (e.g., IL-6, TNF-α) that support T-cell activation and help sustain the chronic inflammatory milieu in HT [130].

4.5 Cytotoxic T Lymphocytes and Thyroid Destruction

$CD8^+$ cytotoxic T lymphocytes (CTLs) infiltrate the thyroid and induce follicular cell death via perforin/granzyme release and Fas/FasL interactions [133]. Flow-cytometry studies show increased perforin expression in $CD8^+$ cells in HT patients, supporting direct CTL-mediated cytotoxicity [134]. These CTLs also produce inflammatory cytokines that amplify tissue injury and contribute to progressive thyroid atrophy and fibrosis, typical histopathological features of HT [133].

4.6 Role of Apoptosis and Oxidative Stress

Enhanced apoptosis of thyrocytes is a hallmark of HT progression. Environmental factors (e.g., excess iodine, toxins) and inflammatory cytokines initiate oxidative stress, generating reactive oxygen species (ROS). ROS upregulate Fas expression on thyrocytes, increasing susceptibility to FasL-mediated apoptosis 135]. In the NOD.H2^{h4} mouse model, excess iodine induced ROS production that increased ICAM-1 expression and thyrocyte apoptosis—effects blocked by NADPH oxidase inhibitors [135]. Clinical studies confirm that oxidative stress markers are elevated in HT and correlate with autoantibody titres [130,135]. Incomplete clearance of apoptotic thyrocytes may lead to secondary necrosis and release of intracellular thyroid antigens, fueling further immune activation and disease perpetuation [135].

4.7. Epigenetic Regulation of Immune Responses

Emerging evidence underscores the pivotal role of epigenetic modifications—including DNA methylation, histone tail alterations, and microRNA-mediated regulation—in modulating immune responses in Hashimoto's thyroiditis (HT) [136,137]. Aberrant DNA methylation patterns in key immune-regulatory genes, such as *FOXP3* and *CTLA-4*, have been associated with diminished regulatory T cell (Treg) function, thereby promoting autoimmune reactivity [138]. Concurrently, dysregulated expression of specific microRNAs, notably miR-155 and miR-146a, has been implicated in altered cytokine secretion and lymphocyte activation, contributing to a pro-inflammatory milieu [139]. Environmental exposures, including viral infections and xenobiotic compounds,

may act as epigenetic modulators, bridging genetic susceptibility with environmental factors in the pathogenesis of HT [140]. These modifications often result in sustained immune activation and perpetuation of autoimmunity.

4.8. Fibrosis and Tissue Remodeling

Prolonged inflammation in HT initiates fibrotic remodeling of the thyroid parenchyma. The recruitment and activation of fibroblasts and myofibroblasts are driven predominantly by pro-fibrotic cytokines such as transforming growth factor-beta (TGF-β) and interleukin-13 (IL-13), which stimulate the deposition of extracellular matrix components [141]. This process leads to progressive architectural distortion, glandular atrophy, and loss of functional thyroid follicles. The resulting fibrosis not only contributes to the mechanical shrinkage of the gland but also impairs hormone production, exacerbating hypothyroidism in affected individuals [142].

4.9. Conclusion of section

The immunopathogenesis of HT can be conceptualized as a multi-phase cascade involving both innate and adaptive immune components: genetic susceptibility coupled with environmental triggers (e.g., infections, toxins) precipitates the breakdown of central and peripheral immune tolerance. Activation of antigen-presenting cells (APCs) and aberrant expression of HLA molecules by thyroid follicular cells enable presentation of thyroid antigens. A predominance of Th1 and Th17 immune responses leads to secretion of pro-inflammatory cytokines such as IFN-γ, TNF-α, and IL-17. B cell activation results in the generation of autoantibodies targeting thyroid peroxidase (TPO) and thyroglobulin (Tg), contributing to antibody-dependent cytotoxicity. Cytotoxic $CD8^+$ T lymphocytes (CTLs) mediate apoptosis of thyrocytes via perforin/granzyme and Fas–FasL pathways. Oxidative stress and persistent epigenetic dysregulation reinforce the inflammatory circuit and sustain tissue damage.Chronic immune activity culminates in fibrosis and tissue remodeling, ultimately resulting in irreversible destruction of thyroid tissue and clinical hypothyroidism.

RESULTS

Recent studies confirm that Hashimoto's thyroiditis (HT) arises from a multifactorial combination of genetic, environmental, and immunological factors. Specific gene polymorphisms—particularly in HLA-DRB1, CTLA-4, PTPN22, and FOXP3—increase the risk of autoimmunity by weakening immune tolerance. Environmental triggers such as excessive iodine intake, vitamin D deficiency, viral infections (e.g., Epstein-Barr virus, Hepatitis C, SARS-CoV-2), gut dysbiosis, and exposure to endocrine disruptors (e.g., bisphenol A, phthalates) are associated with increased disease onset and severity. These factors contribute to the dysregulation of immune homeostasis, loss of self-tolerance, and the development of autoantibodies against thyroglobulin (Tg) and thyroid peroxidase (TPO). Immunologically, HT is characterized by dominant Th1 and Th17 responses, impaired Treg activity, increased antigen presentation by thyrocytes, and cytotoxic CD8+ T-cell-mediated apoptosis of thyroid tissue. These responses are further amplified by oxidative stress and pro-inflammatory cytokines like IFN-γ, IL-6, and IL-17, contributing to progressive thyroid destruction.

CONCLUSIONS

Hashimoto's thyroiditis (HT) represents a complex organ-specific autoimmune disease resulting from a dynamic interplay between genetic susceptibility, environmental exposures, epigenetic dysregulation, and immune system imbalance. While key genetic loci such as *HLA-DRB1*, *CTLA-4*, and *PTPN22* confer increased risk, they do not act in isolation. Environmental triggers—including excessive iodine intake, viral infections, psychosocial stress, and exposure to endocrine-disrupting chemicals—modulate immune tolerance and contribute to disease initiation and progression. Additionally, epigenetic mechanisms (e.g., DNA methylation, histone modifications, and non-coding RNAs) serve as crucial mediators linking environmental stimuli with gene expression changes in immune and thyroid cells.Despite advances in our understanding of HT's immunopathogenesis, many unanswered questions remain. The heterogeneity in clinical presentation, progression rate, and therapeutic response among affected individuals underscores the need for personalized medicine approaches. Future research should prioritize large-scale, longitudinal multi-omic studies (genomic, epigenomic, transcriptomic, proteomic, and metabolomic) to construct robust risk prediction models and to identify reliable biomarkers for early detection, disease staging, and therapy monitoring.Preventive strategies such as selenium and vitamin D supplementation have shown potential in modulating autoimmunity and reducing disease severity in early-stage HT, but require validation through high-quality randomized controlled trials. Similarly, the influence of the gut microbiome on immune tolerance and thyroid function is an emerging field with therapeutic implications. Microbiome-targeted interventions—such as probiotics, prebiotics, and fecal microbiota transplantation—may offer novel avenues for immune modulation in HT. Furthermore, fetal microchimerism, a phenomenon involving the persistence of fetal cells in maternal tissues, is increasingly recognized as a possible contributor to autoimmune thyroid disease in women and merits deeper investigation. Ultimately, the integration of molecular insights, environmental epidemiology, and systems immunology will pave the way for precision prevention and targeted therapies in Hashimoto's thyroiditis. Interdisciplinary collaboration across immunology, endocrinology, genetics, and bioinformatics is essential to transform these research insights into clinical interventions that can halt or reverse disease progression, improve quality of life, and reduce long-term complications. HT results from interplay between inherent genetic risk and environmental factors, mediated through epigenetic and immune disruptions. Promising interventions include selenium and vitamin D supplementation trials as preventive measures. Future research should involve large-scale multi-omic profiling to enable personalized risk stratification and targeted therapies. Further exploration of microchimerism, epigenomics, and microbiome-targeted interventions is warranted.

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