Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: June 30, 2024

Citation: Rodriguez-Reyes, D., et al., 2024. Hashimoto thyroiditis in pediatrics: insights into pathogenesis, diagnosis, and management with considerations of cancer risk. Medical Research Archives, [online] 12(6). https://doi.org/10.18103/mra.v12i6.5427

DOI: https://doi.org/10.18103/mra.v12i6.5427

ISSN: 2375-1924

REVIEW ARTICLE

HASHIMOTO THYROIDITIS IN PEDIATRICS: INSIGHTS INTO PATHOGENESIS, DIAGNOSIS, AND MANAGEMENT WITH CONSIDERATIONS OF CANCER RISK

Derick Rodriguez-Reyes[1], Humberto Lugo-Vicente[2*], Jose I. Acosta-Julbe[1], José Cruz-García[1]

[1]UPR School of Medicine, San Juan, Puerto Rico.
[2]Section of Pediatric Surgery, Department of Surgery, UPR School of Medicine, San Juan, Puerto Rico.

[*]humberto.lugo@upr.edu

ABSTRACT

This systematic review comprehensively examines the pathogenesis, diagnosis, management, and cancer risk of Hashimoto's thyroiditis in pediatric populations. We searched the literature using PubMed, Web of Science, and critical medical journals, focusing on studies published within a specified timeframe. Inclusion criteria targeted studies on pediatric populations, while exclusion criteria filtered out irrelevant studies. Data extraction and synthesis highlighted key findings: genetic predispositions and environmental triggers such as selenium levels and gut microbiota alterations contribute to Hashimoto's Thyroiditis pathogenesis. Diagnostic challenges arise from the often subtle and nonspecific clinical presentation, necessitating thorough clinical evaluations and diagnostic testing, including TSH, free T4, thyroid antibodies, and ultrasound. Management strategies involve levothyroxine therapy, dietary considerations, and lifestyle modifications tailored to individual patient needs. Additionally, the review discusses the controversial but significant potential association between Hashimoto's Thyroiditis and increased thyroid cancer risk, emphasizing the need for vigilant long-term monitoring. This synthesis provides critical insights to inform clinical practice and future research directions.

Introduction

Hashimoto's Thyroiditis (HT), also known as chronic lymphocytic thyroiditis, is a significant autoimmune disorder characterized by thyroid gland inflammation, which commonly leads to hypothyroidism. However, it can also present with thyroid enlargement (goiter), nodules, and, in rare cases, transient hyperthyroidism, along with various associated symptoms such as fatigue, weight gain, cold intolerance, dry skin, and depression. The disease bears the name of Hakaru Hashimoto, a Japanese physician who, in 1912, provided the seminal description of the characteristic lymphocytic infiltration and thyroid gland destruction observed in affected individuals. Since then, our understanding of HT has deepened, revealing a complex interplay of genetic, environmental, and immunological factors in its pathogenesis. While typically associated with adults, its occurrence in pediatric populations is increasingly recognized, posing unique challenges in diagnosis and management. Recent advancements have shed light on various aspects of Hashimoto's disease in children, prompting a deeper exploration of its pathogenesis, diagnosis, management, and potential implications, including cancer risk[1-3].

Understanding the intricate interplay of immune dysregulation and genetic predisposition in developing HT is fundamental. In pediatric cases, the mechanisms underlying this autoimmune thyroiditis remain an area of active investigation, focusing on elucidating the triggers and pathways involved in disease initiation and progression. The diagnosis of HT in pediatric patients presents distinct challenges due to its often subtle and nonspecific clinical presentation. Differentiating between typical childhood symptoms and those indicative of thyroid dysfunction requires a nuanced approach, emphasizing the importance of comprehensive clinical evaluation and appropriate diagnostic testing. Management strategies for pediatric Hashimoto's disease encompass pharmacological and non-pharmacological interventions aimed at restoring thyroid function and alleviating symptoms. Tailoring treatment plans to individual patient needs is paramount, considering age, disease severity, comorbidities, and patient preferences[4-6].

Beyond its immediate impact on thyroid function and overall well-being, HT in pediatric patients raises concerns regarding long-term health outcomes, including the potential risk of thyroid cancer. While the association between autoimmune thyroiditis and thyroid malignancies is documented, it is still a controversial topic that warrants further investigation. Understanding the relationship between pediatric HT and increased cancer risk is essential for informing surveillance strategies and optimizing patient outcomes[7-9]. In light of these considerations, this paper aims to provide comprehensive insights into HT in pediatrics, spanning its pathogenesis, diagnosis, management, and implications for cancer risk. By addressing these critical aspects, this research seeks to enhance our understanding of pediatric autoimmune thyroiditis and inform current evidence-based approaches to its diagnosis, management, and long-term surveillance.

Methodology

We systematically gathered, analyzed, and synthesized relevant literature on Hashimoto's

Thyroiditis (HT) in pediatric populations, focusing on pathogenesis, diagnosis, management, and considerations of cancer risk, while applying specific exclusion criteria and adhering to a defined time-frame and inclusion criteria for this review. Our search strategy encompassed critical databases such as PubMed, Web of Science, and relevant medical journals, utilizing search terms like "Hashimoto's disease," "pediatrics," "pathogenesis," "diagnosis," "management," and "cancer risk." Inclusion criteria included studies published between 1990 and 2023 that focus on pediatric populations (ages 0-18) diagnosed with HT, addressing aspects such as pathogenesis, diagnostic methods, management strategies, or the risk of developing thyroid cancer. Exclusion criteria included studies with sample sizes smaller than 10 participants, studies not peer-reviewed, studies focusing exclusively on adult populations, or studies lacking specific data on the pediatric presentation, diagnosis, or management of HT. Retrieved articles were screened based on titles and abstracts, followed by a full-text assessment that met our inclusion and exclusion criteria. Data extraction involved systematically extracting relevant information from selected studies, including key findings, methodologies, and conclusions. Synthesis and analysis of the extracted data were performed to identify trends, knowledge gaps, and areas for further investigation. The review is structured to present findings in sections corresponding to the main themes: pathogenesis, diagnosis, management, and considerations of cancer risk. Finally, the review concludes with a comprehensive literature synthesis, highlighting key insights and implications for clinical practice and future research directions.

PATHOGENESIS OF HASHIMOTO'S DISEASE:

Hashimoto's Thyroiditis (HT) in pediatric patients represents a complex interplay of genetic predispositions, environmental influences, and dysregulated immune responses, ultimately leading to chronic inflammation and tissue damage within the thyroid gland. The intricate balance between genetic susceptibility and environmental triggers is highlighted in the comprehensive understanding of the disease's etiology and risk factors. Notably, a large Swedish twin study revealed a probands concordance rate for HT of 0.29 and 0.1 for monozygotic and dizygotic twins, respectively, estimating a heritability of 0.64[10]. Although this heritability is lower than that observed for other autoimmune conditions like type 1 diabetes mellitus and Addison's disease, it underscores the significant genetic component in HT susceptibility. While familial coaggregation with other autoimmune diseases is less common than anticipated, the higher concordance rates in monozygotic twins emphasize the role of shared genes in disease predisposition[11]. Research efforts have focused on identifying specific genetic variations associated with HT, with studies implicating genes encoding proteins such as thyroglobulin and tumor necrosis factor-α-induced protein 3 (A20) in the disease process[12]. Despite these advancements, the contribution of established genetic polymorphisms to HT variability remains modest, suggesting the involvement of numerous genes, each exerting a negligible effect on disease susceptibility. Moreover, emerging evidence indicates the existence of rare genetic variants contributing to HT risk, as demonstrated by the identification of novel

splice site variants in genes like thyroglobulin and A20[13]. Consanguinity has also been linked to an increased relative risk of HT, particularly in autosomal recessive disorders, further highlighting the multifaceted nature of genetic influences on disease susceptibility[14]. Additionally, candidate gene association studies have identified potential genetic candidates, such as the tumor necrosis factor superfamily member four genes, implicating co-stimulatory signals in HT pathogenesis[15]. However, the complexity of genetic interactions and the need for larger, well-controlled studies underscore the ongoing challenges in unraveling the genetic basis of HT and its interplay with environmental factors[16-20].

Environmental factors exert a significant influence on the susceptibility to Hashimoto's thyroiditis, intricately intertwining with genetic predispositions to orchestrate disease progression. Among these factors, selenium has garnered considerable attention as a potential therapeutic agent despite conflicting evidence regarding its efficacy. Studies investigating the association between selenium intake and autoimmune thyroiditis markers and the effects of selenium supplementation have yielded inconsistent results, underscoring the complexity of its role in HT management[21]. Moreover, seasonal variations, exemplified by the heightened risk of HT among individuals born in the summer, point towards the potential impact of environmental exposures, such as infectious agents or vitamin D levels, on disease development[22]. Additionally, alterations in gut microbiota composition have emerged as a compelling area of research, with growing evidence implicating dysbiosis in HT pathogenesis[23]. While studies have identified changes in gut microbiota in both hypothyroid and euthyroid HT patients, further investigations are warranted to elucidate the causal relationship between gut dysbiosis and HT susceptibility[24]. Furthermore, medications modulating the immune system, including α-interferon and immune checkpoint inhibitors, have been implicated as potential triggers for HT onset or exacerbation[25-31].

The intricate interplay between immune dysregulation and environmental exposures underscores the multifactorial nature of HT etiology, necessitating comprehensive research efforts to unravel the precise mechanisms underlying ecological contributions to disease pathogenesis and their therapeutic implications in HT management[20].

The complex pathogenesis of autoimmune thyroiditis, encompassing both goitrous and atrophic forms, has been a subject of extensive debate, particularly regarding whether these manifestations represent a continuum or discrete entities. A significant aspect contributing to this debate is IgG4-related disease (IgG4-RD), a recently recognized disorder characterized by IgG4-positive plasma cell infiltration, stromal fibrosis, and elevated serum IgG4 concentrations[32]. Notably, while approximately 30% of HT patients in Japan and the United States exhibit IgG4-RD affecting the thyroid, the prevalence is notably lower in Europe, hinting at potential regional variations or methodological disparities. Regulatory T cells (Treg) play a pivotal role in immune regulation, yet abnormalities in Treg subsets have been documented in HT, suggesting a breakdown in immune tolerance mechanisms[32]. Moreover, cytokine-mediated pathways, including Th17 cell involvement and

inflammasome activation, contribute to the inflammatory milieu within the thyroid gland, perpetuating autoimmune responses. The PD-1/PD ligand-1 axis, known for its role in immune homeostasis, has also garnered attention, particularly in the context of thyroid follicular cell expression and its potential implications for autoimmune reactions[33-41]. Thyroid autoantibodies, although not essential for HT initiation, correlate with symptomatology and impaired quality of life, indicating a direct impact of autoimmunity on patient well-being[38,42-44]. Notably, interventions aimed at suppressing the autoimmune process, such as thyroidectomy, have shown promise in ameliorating symptoms and improving patient outcomes. Additionally, thyroid-stimulating hormone receptor (TSHR) antibodies in HT patients underscore their role in thyroid dysfunction and their potential association with thyroid-associated ophthalmopathy[45-47]. Unraveling the intricate interplay of immune mechanisms in HT offers insights into disease progression. It highlights avenues for targeted therapeutic interventions to modulate autoimmune responses and improve patient outcomes[20].

CLINICAL PRESENTATION AND DIAGNOSIS OF HASHIMOTO DISEASE IN INFANTS, CHILDREN, AND ADOLESCENTS:

Hashimoto's Thyroiditis (HT) is an acquired disease where one develops autoantibodies in the thyroid gland. HT can be diagnosed by the presence of thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TGAb) and may also be confirmed by typical alterations observed in thyroid ultrasound. It is the most common cause of hypothyroidism in pediatric patients, with a prevalence of approximately 1% worldwide. Incidence increases gradually with age, peaking in adolescence. Nevertheless, HT can rarely occur in infants and neonates aged three years and younger, and the presentation can be distinct. According to several reported case studies and a recent cross-sectional study, acquired hypothyroidism via HT is rare in patients under three years old[48-52]. In a recent cross-sectional study, pediatric patients in a hospital group who developed HT over 10 years were analyzed for patient characteristics, presenting symptoms, and overall longitudinal care. The proportion of children under three years of age was 1.15%. For this young patient population, the most common reasons for doctor visits were thyroid enlargement, global developmental delay, and routine functional thyroid testing in patients with type 1 diabetes (T1DM)[52]. Identifying these signs early, along with other signs of possible hypothyroidism, including short stature and poor appetite, warrants closer examination at this age to begin thyroid replacement therapy as soon as possible.

Congenital hypothyroidism, distinct from acquired hypothyroidism, is screened for in many countries via measurement of TSH and T4 levels at 2-5 days of age[3]. TPOAb or TGAb Findings in neonatal testing are often due to placental transference, which represents a transient rise in antithyroid antibodies, as opposed to congenital HT of the newborn[53].

Development of antithyroid antibodies in child and adolescent patients can manifest with various signs and symptoms, often reflecting the thyroid status at diagnosis. Pediatric patients with HT may present with no apparent symptoms besides goiter, which a family member or a caregiver may initially notice or find incidentally on a physical exam for unrelated medical evaluations[4,54]. Symptomatic presentation is

less frequent than asymptomatic presentation, with goiter often being the primary reason for referral in one study group and more significant than half of patients presenting without symptoms in another[54,55]. Importantly, thyroid function at presentation can vary significantly among pediatric reports, spanning from euthyroidism to overt hypothyroidism or, less commonly, transient hyperthyroidism termed hashitoxicosis[54,55]. The presentation of hashitoxicosis can resemble that of Graves' disease, with symptoms such as goiter, tachycardia, tremor, weight loss, restlessness, warm, moist skin, ophthalmopathy, growth acceleration, and delayed or precocious puberty.

The most common manifestation of hypothyroidism in pediatric patients, aside from goiter, is decreased height velocity, which may be insidious in onset[55]. Skeletal maturation should be assessed and monitored longitudinally via the determination of bone age. Other common manifestations include those commonly associated with hypothyroidism, including constipation, weight gain, fatigue, drowsiness, poor school performance, cold intolerance, dry skin, bradycardia, and a yellowish-pale skin tone with facial puffiness (myxedema). Additionally, symptoms such as delayed or arrested pubertal development, irregular menstrual periods, menometrorrhagia, or amenorrhea may be observed in adolescents with overt hypothyroidism[56,57].

DIAGNOSIS OF HASHIMOTO THYROIDITIS

Deciding to test for thyroid dysfunction depends on clinical findings as described above, namely, goiter, most commonly, irregularities upon palpation of the thyroid gland, or symptoms associated with hypo- or hyperthyroidism. The most common etiology of thyroid dysfunction in these cases is hypothyroidism, which is typically diagnosed with elevated TSH and decreased thyroid hormones T3/T4[3]. If the etiology is uncertain based on thyroid hormone levels and TSH, the gold standard for diagnosing HT is presence of antithyroid antibodies, TPOAb, and TGAb[58]. Regardless of symptoms, among pediatric patients with HT, up to 95% have circulating antithyroid antibodies, with another small percentage having TSH-receptor-blocking antibodies[58]. Although it is typically unnecessary to diagnose HT via imaging if circulating antithyroid antibodies are found, antibody-negative cases may be confirmed via ultrasound (US). US findings of HT include parenchymal hypoechogenicity, coarse echotexture, and micro nodulation[59]. Although imaging is not necessarily indicated for diagnosis, it is recommended to follow young patients recently diagnosed with HT, even if they are euthyroid, as some go on to develop identifiable US findings along with progression to a hypothyroid state[3].

MANAGEMENT OF HASHIMOTO'S DISEASE IN PEDIATRIC PATIENTS EMERGENT CARE

Treatment and management of Hashimoto's disease, or autoimmune thyroiditis, in pediatric patients, involves carefully considering thyroid hormone levels and individual patient factors. Hashitoxicosis, representing hyperthyroidism secondary to autoimmune destruction of the thyroid gland, usually self-resolves without consequences if the presentation is mild. In more severe cases, often present in patients with higher levels of TPOab, the hyperthyroid phase may require emergent treatment with methimazole or β-blockers[54,59,60]. Other instances that require emergent care include "Hashimoto encephalopathy," which results in fluctuating

neurological and neuropsychological deficits that may progress to seizures. Prompt identification of this complication is essential, as clinicians may order extensive imaging and testing to identify the etiology when this particular condition is very responsive to corticosteroid therapy[61].

PHARMACOLOGICAL INTERVENTIONS

Recommendations from the American Thyroid Association Task Force on Thyroid Hormone Replacement provide a framework for addressing different presentations of HT. For overt hypothyroidism, characterized by elevated serum TSH levels and low free thyroxine (fT4) levels, the primary treatment approach is levothyroxine (LT4) supplementation. The goal of therapy is to alleviate symptoms of hypothyroidism, normalize metabolic parameters, and restore TSH levels to within the reference range for age. LT4 therapy is typically lifelong, although some pediatric patients with Hashimoto's thyroiditis may eventually achieve euthyroidism without the need for continued hormone replacement[4]. In cases of subclinical hypothyroidism, where TSH levels are elevated, but fT4 levels are within the normal range, the decision to initiate LT4 therapy is less straightforward. While some practitioners advocate for LT4 supplementation in this scenario to prevent progression to overt hypothyroidism and alleviate symptoms, others may opt for close monitoring with serial thyroid function tests. Factors such as the degree of TSH elevation, presence of symptoms, and patient age may influence the decision-making process.

Additionally, pediatric patients with comorbid conditions or medications that may affect LT4 absorption or metabolism should be given special consideration[62]. In cases of hyperthyroidism, such as hashitoxicosis, treatment may involve the use of beta-blockers to alleviate symptoms of thyrotoxicosis. However, the management of hyperthyroidism in pediatric patients with Hashimoto's disease may require careful monitoring and potentially the use of antithyroid medications if symptoms persist or worsen. Thyroid hormone replacement therapy may not always be necessary in these cases, especially if the hyperthyroid state is transient. Close follow-up with thyroid function tests is essential to guide treatment decisions and ensure optimal outcomes for these patients[63,64].

When considering discontinuation of hormone replacement therapy, decisions should be made on a case-by-case basis, taking into account factors such as the underlying cause of hypothyroidism, duration of therapy, and patient response to treatment. Some pediatric patients with Hashimoto's disease may achieve euthyroidism spontaneously or with medical intervention and may be candidates for discontinuation of LT4 therapy under close supervision. However, regular monitoring of thyroid function is essential to detect any recurrence of hypothyroidism and ensure timely intervention if needed[64,65].

In pediatric patients with Hashimoto's disease who develop cancer, such as differentiated thyroid cancer (DTC), the management approach may differ. Total thyroidectomy followed by LT4 replacement therapy is the standard treatment for DTC to achieve TSH suppression to reduce the risk of recurrence or progression of the disease. Monitoring for recurrence or metastasis of thyroid cancer is essential in these patients, and regular surveillance with imaging studies and thyroid function tests is recommended. Additionally, special consideration should be given to the

potential impact of thyroid hormone therapy on cancer outcomes and the need for individualized treatment approaches in pediatric patients with Hashimoto's disease and concurrent cancer[66,62].

COMPLICATIONS AND COMORBIDITIES

Since around 20% of patients with Hashimoto develop hypothyroidism and require thyroid hormone replacement therapies (HRT), most experience catch-up growth during adolescence[67]. Severe hypothyroidism often leads to a slowdown, and catch-up growth is one of the main goals of HRTs[68-70]. In addition, a common neurodevelopmental outcome is Hashimoto encephalopathy, which is known as a steroid-responsive encephalopathy associated with high titers of antithyroid antibodies[70]. The prevalence is estimated at around 2 of every 100,000 subjects[70]. The symptoms vary from behavioral and cognitive changes, myoclonus, and seizures to psychosis and coma[70]. Other comorbidities of patients with Hashimoto in pediatric populations are the development of non-thyroid autoimmune diseases and thyroid cancer in a minority of cases[71].

ASSOCIATION BETWEEN HASHIMOTO'S DISEASE AND THYROID CANCER:

Few studies have assessed the associations between Hashimoto and thyroid cancer[72-79]. Most have noted a coexistence between thyroid tumors and Hashimoto and that developing thyroid cancer is more common in patients with Hashimoto than those without[72-79]. A meta-analysis conducted by Lee et al. found that the frequency of Hashimoto in patients with Papillary Thyroid Cancer was around 23%[80]. They found a stronger association with females and a more favorable outcome than patients without Hashimoto[80]. Another study conducted by Erbas et al. found that from 224 children with Hashimoto, 13% had nodules on US follow-up, and 10.3% of those with nodules had papillary thyroid carcinoma (n=3)[81]. Lai et al. found that variations in diagnostic methods affect the rate of prevalence of thyroid disease in patients with Hashimoto; they found a prevalence ranging from 1 to 40%[82]. They also observed an odds risk ratio of 2.12 for Hashimoto developing thyroid cancer[82].

Moreover, the prognosis of the thyroid cancer developed in patients with Hashimoto was not defined. Iliadou et al. found that Hashimoto's was associated with more severe clinical manifestations of the neoplasm, such as the infiltration of the parenchyma and invasive characteristics[83]. However, the presence of Hashimoto did not affect the prognosis, as noted by a follow-up of five to 10 years[83]. Similarly, Ren et al. found a strong association between Hashimoto and cancer[84]. They found no differences (between non-Hashimoto versus Hashimoto patients) in tumor multifocality, tumor size, extrathyroidal infiltration, or metastasis[84].

Several hypotheses have been proposed for this association. One of them is the level of TSH; Golbert et al. found that the risk of malignancy was around three times higher in patients with TSH levels greater than 2.25 micro IU/mL than those with lower TSH (P=0.001)[85]. However, it is unclear whether TSH promotes the development of pre-formed cancer or the development of the tumor itself. Another hypothesis is the role of chronic inflammation secondary to autoimmunity. Hashimoto encourages the development of Thyroglobulin antibodies and thyroid microsomal antibodies (TM-Ab), which are associated with

worse cytological findings than those without these markers[86]. The third hypothesis is gene expression; multiple studies have found an association between RET/PTC rearrangements and high TSH levels[87]. Moreover, more frequently observed in patients with PTC associated with Hashimoto than in PTC without Hashimoto[88]. Lastly, the association between thyroid cancer and Hashimoto is stronger in patients with diabetes type 1 and autoimmune polyglandular syndrome type II, suggesting mutations in proto-oncogenes involved in the pathogenesis of papillary thyroid cancer[89,90].

Results

Genetic predispositions and environmental triggers play significant roles in the development of Hashimoto's Thyroiditis (HT) in pediatric populations. A large Swedish twin study reported a heritability estimate of 0.64 for HT, highlighting the genetic component in disease susceptibility. Candidate gene studies identified several genetic variations, such as those encoding thyroglobulin and TNF-α-induced protein 3 (A20). Environmental factors, such as selenium levels, seasonal variations, and gut microbiota alterations, also contribute to HT pathogenesis. Notably, selenium supplementation showed inconsistent results in managing HT, and changes in gut microbiota composition were observed in HT patients. HT in pediatric patients often presents with subtle and nonspecific symptoms, making diagnosis challenging. The presence of thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TGAb) are key diagnostic markers. Ultrasound findings, such as parenchymal hypoechogenicity and coarse echotexture, support diagnosis in antibody-negative cases. In a cross-sectional study, children under three years of age presented with thyroid enlargement, developmental delay, and type 1 diabetes mellitus (T1DM).

Management strategies for pediatric HT include levothyroxine (LT4) therapy, dietary modifications, and lifestyle adjustments. LT4 therapy is the primary treatment for overt hypothyroidism, while subclinical hypothyroidism may be managed with close monitoring. Beta-blockers are used to manage symptoms of thyrotoxicosis. The American Thyroid Association Task Force on Thyroid Hormone Replacement recommends LT4 supplementation to normalize TSH levels and alleviate hypothyroid symptoms. Approximately 20% of pediatric HT patients develop hypothyroidism requiring hormone replacement therapy (HRT). Neurodevelopmental complications, such as Hashimoto encephalopathy, and other autoimmune diseases are common comorbidities. The prevalence of Hashimoto encephalopathy is approximately 2 per 100,000. Several studies reported an increased risk of thyroid cancer in pediatric HT patients. A meta-analysis found a 23% prevalence of HT in patients with papillary thyroid cancer (PTC), with a stronger association in females. A study by Erbas et al. found that 13% of children with HT had nodules on ultrasound, and 10.3% of those with nodules had PTC. Higher TSH levels were associated with increased cancer risk, and chronic inflammation from autoimmunity was implicated in cancer development.

Discussion

The results underscore the multifactorial nature of Hashimoto's Thyroiditis (HT) pathogenesis in pediatric populations, involving a complex interplay of genetic and environmental factors. The high heritability estimate highlights the

significant genetic component, with specific gene variations implicated in disease susceptibility. However, the modest contribution of individual polymorphisms suggests the involvement of multiple genes. Environmental triggers, such as selenium levels and gut microbiota, further complicate the disease's etiology, necessitating comprehensive research to elucidate their precise roles.

Diagnosing Hashimoto's Thyroiditis in children is challenging due to its often subtle and nonspecific clinical presentation. The presence of TPOAb and TGAb remains crucial for diagnosis, while ultrasound serves as a supportive tool, especially in antibody-negative cases. Early identification and differentiation from typical childhood symptoms are vital for timely intervention and management. Effective management of pediatric HT requires a tailored approach, considering individual patient needs and disease severity. LT4 therapy remains the cornerstone for treating overt hypothyroidism, while subclinical cases warrant close monitoring. The role of dietary and lifestyle modifications, although secondary, is essential for overall well-being. The management of thyrotoxicosis and Hashimoto encephalopathy highlights the need for emergent care and prompt intervention to prevent severe complications.

The potential association between HT and increased thyroid cancer risk in pediatric patients is a significant concern. The higher prevalence of thyroid malignancies in HT patients and the strong association with higher TSH levels underscore the need for vigilant long-term monitoring. Understanding the mechanisms linking chronic inflammation and autoimmunity to cancer development is crucial for optimizing surveillance strategies and improving patient outcomes.Future research should focus on large-scale genetic studies to identify novel variants contributing to HT susceptibility and elucidate the gene-environment interactions in disease pathogenesis. Additionally, exploring the therapeutic potential of selenium and gut microbiota modulation could provide new insights into managing HT. Longitudinal studies are necessary to clarify the cancer risk in pediatric HT patients and develop evidence-based surveillance protocols.

This systematic review provides comprehensive insights into the pathogenesis, diagnosis, management, and cancer risk of Hashimoto's Thyroiditis in pediatric populations. Understanding the intricate interplay of genetic and environmental factors is fundamental to improving diagnostic and therapeutic strategies. Vigilant long-term monitoring is essential to address the potential increased cancer risk and ensure optimal patient outcomes.

Conclusion

This systematic review elucidates the complex nature of genetic and environmental factors in the pathogenesis of Hashimoto's disease in pediatric populations. The diagnosis of HD in children is often challenging due to its variable presentation, ranging from euthyroidism to overt hypothyroidism or, rarely, hyperthyroidism. Effective management strategies, including levothyroxine therapy and regular monitoring, are crucial for maintaining thyroid function and overall well-being. The potential increased risk of thyroid cancer in pediatric HD patients, as evidenced by studies showing higher malignancy rates and more severe clinical manifestations,

underscores the importance of long-term surveillance. Further research is needed to explore these associations and to develop optimized evidence-based management protocols. This review deepens our understanding of pediatric HD, offering a basis for more effective diagnostic and therapeutic strategies in clinical practice.

Conflict of Interest:

None.

Funding:

None.

Acknowledgements:

None.

References:

1. Mincer DL, Jialal I. Hashimoto Thyroiditis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 29, 2023.

2. Hiromatsu Y, Satoh H, Amino N. Hashimoto's thyroiditis: history and future outlook. Hormones (Athens). 2013;12(1):12-18. doi:10.1007/BF03401282.

3. Leung AKC, Leung AAC. Evaluation and management of the child with hypothyroidism. World J Pediatr. 2019;15(2):124-134. doi:10.1007/s12519-019-00230-w.

4. De Luca F, Santucci S, Corica D, et al. Hashimoto's thyroiditis in childhood: presentation modes and evolution over time. Ital J Pediatr. 2013;39(1):8. doi:10.1186/1824-7288-39-8.

5. Ilicki A, Marcus C, Karlsson FA. Hyperthyroidism and hypothyroidism in monozygotic twins: detection of stimulating and blocking TSH receptor antibodies using the FRTL5-cell line. J Endocrinol Invest. 1990;13(4):327-331. doi:10.1007/BF03349571.

6. Wasniewska M, Vigone MC, Cappa M, et al. Acute suppurative thyroiditis in childhood: relative frequency among thyroid inflammatory diseases. J Endocrinol Invest. 2007;30(4):346-347. doi:10.1007/BF03346303.

7. Penta L, Cofini M, Lanciotti L, Leonardi A, Principi N, Esposito S. Hashimoto's Disease and Thyroid Cancer in Children: Are They Associated?. Front Endocrinol (Lausanne). 2018;9:565. Published 2018 Oct 9. doi:10.3389/fendo.2018.00565.

8. Hu X, Wang X, Liang Y, et al. Cancer Risk in Hashimoto's Thyroiditis: a Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2022;13:937871. Published 2022 Jul 12. doi:10.3389/fendo.2022.937871.

9. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked?. Free Radic Biol Med. 2010;49(11):1603-1616. doi:10.1016/j.freeradbiomed.2010.09.006.

10. Skov J, Eriksson D, Kuja-Halkola R, et al. Co-aggregation and heritability of organ-specific autoimmunity: a population-based twin study. Eur J Endocrinol. 2020;182(5):473-480. doi:10.1530/EJE-20-0049.

11. Jabrocka-Hybel A, Skalniak A, Piątkowski J, et al. How much of the predisposition to Hashimoto's thyroiditis can be explained based on previously reported associations?. J Endocrinol Invest. 2018;41(12):1409-1416. doi:10.1007/s40618-018-0910-4.

12. Berteau F, Rouvière B, Nau A, et al. A20 haploinsufficiency (HA20): clinical phenotypes and disease course of patients with a newly recognised NF-kB-mediated autoinflammatory disease. Ann Rheum Dis. 2019;78(5):e35. doi:10.1136/annrheumdis-2018-213347.

13. Zaghlol RY, Haghighi A, Alkhayyat MM, et al. Consanguinity and the Risk of Hashimoto's Thyroiditis. Thyroid. 2017;27(3):390-395. doi:10.1089/thy.2016.0495.

14. Hori T, Ohnishi H, Kadowaki T, et al. Autosomal dominant Hashimoto's thyroiditis with a mutation in TNFAIP3. Clin Pediatr Endocrinol. 2019;28(3):91-96. doi:10.1297/cpe.28.91.

15. Song RH, Wang Q, Yao QM, et al. TNFSF4 Gene Variations Are Related to Early-Onset Autoimmune Thyroid Diseases and Hypothyroidism of Hashimoto's Thyroiditis. Int J Mol Sci. 2016;17(8):1369. Published 2016 Aug 20. doi:10.3390/ijms17081369.

16. Brčić L, Barić A, Gračan S, et al. Genome-wide association analysis suggests novel loci for Hashimoto's thyroiditis. J Endocrinol Invest. 2019;42(5):567-576. doi:10.1007/s40618-018-0955-4.

17. Roberts GHL, Santorico SA, Spritz RA. The genetic architecture of vitiligo. Pigment Cell Melanoma Res. 2020;33(1):8-15. doi:10.1111/pcmr.12848.

18. Lo MS, Towne M, VanNoy GE, et al. Monogenic Hashimoto thyroiditis associated with a variant in the thyroglobulin (TG) gene. J Autoimmun. 2018;86:116-119. doi:10.1016/j.jaut.2017.09.003.

19. Wang Y, Zhu YF, Wang Q, et al. The haplotype of UBE2L3 gene is associated with Hashimoto's thyroiditis in a Chinese Han population. BMC Endocr Disord. 2016;16:18. Published 2016 Apr 19. doi:10.1186/s12902-016-0098-6.

20. Weetman AP. An update on the pathogenesis of Hashimoto's thyroiditis. J Endocrinol Invest. 2021;44(5):883-890. doi:10.1007/s40618-020-01477-1.

21. Negro R, Attanasio R, Grimaldi F, Marcocci C, Guglielmi R, Papini E. A 2016 Italian Survey about the Clinical Use of Selenium in Thyroid Disease. Eur Thyroid J. 2016;5(3):164-170. doi:10.1159/000447667.

22. Thvilum M, Brandt F, Brix TH, Hegedüs L. Month of birth is associated with the subsequent diagnosis of autoimmune hypothyroidism. A nationwide Danish register-based study. Clin Endocrinol (Oxf). 2017;87(6):832-837. doi:10.1111/cen.13425.

23. Ishaq HM, Mohammad IS, Guo H, et al. Molecular estimation of alteration in intestinal microbial composition in Hashimoto's thyroiditis patients. Biomed Pharmacother. 2017;95:865-874. doi:10.1016/j.biopha.2017.08.101.

24. Zhao F, Feng J, Li J, et al. Alterations of the Gut Microbiota in Hashimoto's Thyroiditis Patients. Thyroid. 2018;28(2):175-186. doi:10.1089/thy.2017.0395.

25. Faustino LC, Lombardi A, Madrigal-Matute J, Owen RP, Libutti SK, Tomer Y. Interferon-α Triggers Autoimmune Thyroid Diseases via Lysosomal-Dependent Degradation of Thyroglobulin. J Clin Endocrinol Metab. 2018;103(10):3678-3687. doi:10.1210/jc.2018-00541.

26. Urwyler P, Earnshaw I, Bermudez M, et al. Mechanisms of checkpoint inhibition-induced adverse events. Clin Exp Immunol. 2020;200(2):141-154. doi:10.1111/cei.13421.

27. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine Toxicity of Cancer Immunotherapy Targeting Immune Checkpoints. Endocr Rev. 2019;40(1):17-65. doi:10.1210/er.2018-00006.

28. Kotwal A, Gustafson MP, Bornschlegl S, et al. Immune Checkpoint Inhibitor-Induced Thyroiditis Is Associated with Increased Intrathyroidal T Lymphocyte Subpopulations. Thyroid. 2020;30(10):1440-1450. doi:10.1089/thy.2020.0075.

29. Wichman J, Winther KH, Bonnema SJ, Hegedüs L. Selenium Supplementation Significantly Reduces Thyroid Autoantibody Levels in Patients with Chronic Autoimmune Thyroiditis: A Systematic Review and Meta-Analysis. Thyroid. 2016;26(12):1681-1692. doi:10.1089/thy.2016.0256.

30. Winther KH, Rayman MP, Bonnema SJ, Hegedüs L. Selenium in thyroid disorders - essential knowledge for clinicians. Nat Rev

Endocrinol. 2020;16(3):165-176. doi:10.1038/s41574-019-0311-6.

31. Scappaticcio L, Castellana M, Virili C, et al. Alemtuzumab-induced thyroid events in multiple sclerosis: a systematic review and meta-analysis. J Endocrinol Invest. 2020;43(2):219-229. doi:10.1007/s40618-019-01105-7.

32. Jokisch F, Kleinlein I, Haller B, Seehaus T, Fuerst H, Kremer M. A small subgroup of Hashimoto's thyroiditis is associated with IgG4-related disease. Virchows Arch. 2016;468(3):321-327. doi:10.1007/s00428-015-1893-6.

33. Rodríguez-Muñoz A, Vitales-Noyola M, Ramos-Levi A, Serrano-Somavilla A, González-Amaro R, Marazuela M. Levels of regulatory T cells CD69(+)NKG2D(+)IL-10(+) are increased in patients with autoimmune thyroid disorders. Endocrine. 2016;51(3):478-489. doi:10.1007/s12020-015-0662-2.

34. Vitales-Noyola M, Serrano-Somavilla A, Martínez-Hernández R, et al. Patients With Autoimmune Thyroiditis Show Diminished Levels and Defective Suppressive Function of Tr1 Regulatory Lymphocytes. J Clin Endocrinol Metab. 2018;103(9):3359-3367. doi:10.1210/jc.2018-00498.

35. Ajjan RA, Weetman AP. The Pathogenesis of Hashimoto's Thyroiditis: Further Developments in our Understanding. Horm Metab Res. 2015;47(10):702-710. doi:10.1055/s-0035-1548832.

36. Zake T, Skuja S, Kalere I, Konrade I, Groma V. Heterogeneity of tissue IL-17 and tight junction proteins expression demonstrated in patients with autoimmune thyroid diseases. Medicine (Baltimore). 2018;97(25):e11211. doi:10.1097/MD.0000000000011211.

37. Vitales-Noyola M, Ramos-Levi AM, Martínez-Hernández R, et al. Pathogenic Th17 and Th22 cells are increased in patients with autoimmune thyroid disorders. Endocrine. 2017;57(3):409-417. doi:10.1007/s12020-017-1361-y.

38. Guan LJ, Wang X, Meng S, et al. Increased IL-21/IL-21R expression and its proinflammatory effects in autoimmune thyroid disease. Cytokine. 2015;72(2):160-165. doi:10.1016/j.cyto.2014.11.005.

39. Guo Q, Wu Y, Hou Y, et al. Cytokine Secretion and Pyroptosis of Thyroid Follicular Cells Mediated by Enhanced NLRP3, NLRP1, NLRC4, and AIM2 Inflammasomes Are Associated With Autoimmune Thyroiditis. Front Immunol. 2018;9:1197. Published 2018 Jun 4. doi:10.3389/fimmu.2018.01197.

40. Álvarez-Sierra D, Marín-Sánchez A, Ruiz-Blázquez P, et al. Analysis of the PD-1/PD-L1 axis in human autoimmune thyroid disease: Insights into pathogenesis and clues to immunotherapy associated thyroid autoimmunity. J Autoimmun. 2019;103:102285. doi:10.1016/j.jaut.2019.05.013.

41. Marelli-Berg FM, Weetman A, Frasca L, et al. Antigen presentation by epithelial cells induces anergic immunoregulatory CD45RO+ T cells and deletion of CD45RA+ T cells. J Immunol. 1997;159(12):5853-5861.

42. Nishihara E, Amino N, Kudo T, et al. Comparison of thyroglobulin and thyroid peroxidase antibodies measured by five different kits in autoimmune thyroid diseases. Endocr J. 2017;64(10):955-961. doi:10.1507/endocrj.EJ17-0164.

43. Bektas Uysal H, Ayhan M. Autoimmunity affects health-related quality of life in patients with Hashimoto's thyroiditis. Kaohsiung J Med Sci. 2016;32(8):427-433. doi:10.1016/j.kjms.2016.06.006.

44. Barić A, Brčić L, Gračan S, et al. Thyroglobulin Antibodies are Associated with Symptom Burden in Patients with Hashimoto's Thyroiditis: A Cross-Sectional Study. Immunol Invest. 2019;48(2):198-209. doi:10.1080/08820139.2018.1529040.

45. Guldvog I, Reitsma LC, Johnsen L, et al. Thyroidectomy Versus Medical Management for Euthyroid Patients With Hashimoto Disease and Persisting Symptoms: A Randomized Trial. Ann Intern Med. 2019;170(7):453-464. doi:10.7326/M18-0284.

46. Diana T, Krause J, Olivo PD, et al. Prevalence and clinical relevance of thyroid stimulating hormone receptor-blocking antibodies in autoimmune thyroid disease. Clin Exp Immunol. 2017;189(3):304-309. doi:10.1111/cei.12980.

47. Kahaly GJ, Diana T, Glang J, Kanitz M, Pitz S, König J. Thyroid Stimulating Antibodies Are Highly Prevalent in Hashimoto's Thyroiditis and Associated Orbitopathy. J Clin Endocrinol Metab. 2016;101(5):1998-2004. doi:10.1210/jc.2016-1220.

48. Foley TP Jr, Abbassi V, Copeland KC, Draznin MB. Hypothyroidism caused by chronic autoimmune thyroiditis in very young infants. N Engl J Med. 1994;330(7):466-468. doi:10.1056/NEJM199402173300070.

49. Gunther DF, Chiu HK, Numrych TE, Kletter GB. Onset of acquired autoimmune hypothyroidism in infancy: a presentation of delayed gross-motor development and rhabdomyolysis. Eur J Pediatr. 2006;165(5):320-322. doi:10.1007/s00431-005-0051-6.

50. Mittnacht J, Schmidt F, Ebinger F, Bettendorf M. Unusual clinical presentation of primary hypothyroidism in a very young infant caused by autoimmune thyroiditis: case report and update of the literature. Eur J Pediatr. 2007;166(8):881-883. doi:10.1007/s00431-006-0323-9.

51. Marzuillo P, Grandone A, Perrotta S, et al. Very early onset of autoimmune thyroiditis in a toddler with severe hypothyroidism presentation: a case report. Ital J Pediatr. 2016;42:61. doi:10.1186/s13052-016-0270-7.

52. Tang S, Yang M, Zhang D, Tong YJ, Xin Y. Clinical characteristics and follow-up of 19 children with Hashimoto's thyroiditis aged below 3 years: a single-center retrospective analysis. Front Endocrinol (Lausanne). 2021;12:737527. doi:10.3389/fendo.2021.737527.

53. Rose SR, Wassner AJ, Wintergerst KA, et al. Congenital hypothyroidism: screening and management. Pediatrics. 2023;151(1):e2022060419. doi:10.1542/peds.2022-060419.

54. Wasniewska M, Corrias A, Salerno M, et al. Thyroid function patterns at Hashimoto's thyroiditis presentation in childhood and adolescence are mainly conditioned by patients' age. Horm Res Paediatr. 2012;78(4):232-236. doi:10.1159/000343815.

55. de Vries L, Bulvik S, Phillip M. Chronic autoimmune thyroiditis in children and adolescents: at presentation and during long-term follow-up. Arch Dis Child. 2009;94(1):33-37. doi:10.1136/adc.2007.134841.

56. Weber G, Vigone MC, Stroppa L, Chiumello G. Thyroid function and puberty. J Pediatr Endocrinol Metab. 2003;16:253-257.

57. Bauman A, Novello L, Kreitzer P. Endocrine Disorders and Delayed Puberty. In: Abnormal Female Puberty: A Clinical Casebook. 2016:87-107.

58. Wassner AJ. Pediatric Hypothyroidism: Diagnosis and Treatment. *Paediatr Drugs*. 2017;19(4):291-301. doi:10.1007/s40272-017-0238-0

59. Lee SJ, Lim GY, Kim JY, Chung MH. Diagnostic performance of thyroid ultrasonography screening in pediatric patients with a hypothyroid, hyperthyroid or euthyroid goiter. Pediatr Radiol. 2016;46:104-111.

60. Vukovic R, Zeljkovic A, Bufan B, Spasojevic-Kalimanovska V, Milenkovic T, Vekic J. Hashimoto Thyroiditis and Dyslipidemia in Childhood: A Review. Front Endocrinol (Lausanne). 2019;10:868. Published 2019 Dec 10. doi:10.3389/fendo.2019.00868.

61. Watemberg N, Greenstein D, Levine A. Encephalopathy associated with Hashimoto thyroiditis: pediatric perspective. J Child Neurol. 2006;21(1):1-5. doi:10.1177/08830738060210010201.

62. Rodriguez L, Dinauer C, Francis G. Treatment of hypothyroidism in infants, children and adolescents. Trends Endocrinol Metab. 2022;33(7):522-532. doi:10.1016/j.tem.2022.04.007.

63. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid. 2014;24(12):1670-1751. doi:10.1089/thy.2014.0028.

64. Radetti G, Salerno M, Guzzetti C, et al. Thyroid function in children and adolescents with Hashimoto's thyroiditis after l-thyroxine discontinuation. Endocr Connect. 2017;6(4):206-212. doi:10.1530/EC-17-0023.

65. Gopalakrishnan S, Chugh PK, Chhillar M, Ambardar VK, Sahoo M, Sankar R. Goitrous autoimmune thyroiditis in a pediatric population: a longitudinal study. Pediatrics. 2008;122(3):e670-e674. doi:10.1542/peds.2008-0493.

66. Osowiecka K, Myszkowska-Ryciak J. The Influence of Nutritional Intervention in the Treatment of Hashimoto's Thyroiditis-A Systematic Review. Nutrients. 2023;15(4):1041. doi:10.3390/nu15041041.

67. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev. 2014;13(4-5):391-397. doi:10.1016/j.autrev.2014.01.007.

68. Vincent A, Bouvattier C, Teinturier C, et al. Evaluation of catch-up growth in severe pediatric Hashimoto's hypothyroidism. Arch Pediatr. 2023;30(3):142-148. doi:10.1016/j.arcped.2023.01.001.

69. Brain L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. Lancet. 1966;2(7462):512-514. doi:10.1016/s0140-6736(66)92876-5.

70. Mocellin R, Walterfang M, Velakoulis D. Hashimoto's encephalopathy: epidemiology, pathogenesis and management. CNS Drugs. 2007;21(10):799-811. doi:10.2165/00023210-200721100-00002.

71. Ruggeri RM, Trimarchi F, Giuffrida G, Certo R, Cama E, Campennì A, Alibrandi A, De Luca F, Wasniewska M. Autoimmune comorbidities in Hashimoto's thyroiditis: different patterns of association in adulthood and childhood/adolescence. Eur J Endocrinol. 2017;176(2):133-141.

72. Penta L, Cofini M, Lanciotti L, Leonardi A, Principi N, Esposito S. Hashimoto's Disease and Thyroid Cancer in Children: Are They Associated?. Front Endocrinol (Lausanne). 2018;9:565. Published 2018 Oct 9. doi:10.3389/fendo.2018.00565.

73. Keefe G, Culbreath K, Cherella CE, et al. Autoimmune Thyroiditis and Risk of Malignancy in Children with Thyroid Nodules. Thyroid. 2022;32(9):1109-1117. doi:10.1089/thy.2022.0241.

74. Gallant J-N, Weiss VL, Chen SC, Liang J, Belcher RH, Ye F, Correa H, Wang H. Hashimoto's Thyroiditis and the Risk of Papillary Thyroid Cancer in Children. Cancers. 2023;15(19):4902. doi:10.3390/cancers15194902.

75. Gallant JN, Weiss VL, Chen SC, et al. Hashimoto's Thyroiditis and the Risk of Papillary Thyroid Cancer in Children. Cancers (Basel). 2023;15(19):4902. Published 2023 Oct 9. doi:10.3390/cancers15194902.

76. Seppälä LK, Madanat-Harjuoja LM, Leinonen MK, Lääperi M, Vettenranta K. Maternal Thyroid Disease and the Risk of Childhood Cancer in the Offspring. Cancers (Basel). 2021;13(21):5409. Published 2021 Oct 28. doi:10.3390/cancers13215409.

77. Sur ML, Gaga R, Lazăr C, Lazea C, Aldea C, Sur D. Papillary thyroid carcinoma in children with Hashimoto's thyroiditis - a review of the literature between 2000 and 2020. J Pediatr Endocrinol Metab. 2020;33(12):1511-1517. Published 2020 Nov 12. doi:10.1515/jpem-2020-0383.

78. Penta L, Cofini M, Lanciotti L, Leonardi A, Principi N, Esposito S. Hashimoto's Disease and Thyroid Cancer in Children: Are They Associated?. Front Endocrinol (Lausanne). 2018;9:565. Published 2018 Oct 9. doi:10.3389/fendo.2018.00565.

79. Gallant JN, Weiss VL, Chen SC, et al. Hashimoto's Thyroiditis and the Risk of Papillary Thyroid Cancer in Children. Cancers (Basel). 2023;15(19):4902. Published 2023 Oct 9. doi:10.3390/cancers15194902.

80. 80. Lee JH, Kim Y, Choi JW, Kim YS. The association between papillary thyroid carcinoma and histologically proven Hashimoto's thyroiditis: a meta-analysis. Eur J Endocrinol. 2013;168(3):343-349. Published 2013 Feb 15. doi:10.1530/EJE-12-0903.

81. Erbaş İ, Erbaş İ, Evliyaoğlu O. Clinical, biochemical, and radiological follow-up results of children and adolescents with Hashimoto's thyroiditis: a single-center experience. J Pediatr Endocrinol Metab. 2021;34(8):987-994. doi:10.1515/jpem-2021-0035.

82. Lai X, Xia Y, Zhang B, Li J, Jiang Y. A meta-analysis of Hashimoto's thyroiditis and papillary thyroid carcinoma risk. Oncotarget. 2017;8:62414-62424. doi:10.18632/oncotarget.18620.

83. Iliadou PK, Effraimidis G, Konstantinos M, et al. Chronic lymphocytic thyroiditis is associated with invasive characteristics of differentiated thyroid carcinoma in children and adolescents. Eur J Endocrinol. 2015;173(6):827-833. doi:10.1530/EJE-14-1046.

84. Ren PY, Liu J, Xue S, Chen G. Pediatric differentiated thyroid carcinoma: The clinicopathological features and the coexistence of Hashimoto's thyroiditis. Asian J Surg. 2019;42(1):112-119. doi:10.1016/j.asjsur.2017.10.006.

85. Golbert L, de Cristo AP, Faccin CS, et al. Serum TSH levels as a predictor of malignancy in thyroid nodules: A prospective study. PLoS One. 2017;12(11):e0188123. Published 2017 Nov 16. doi:10.1371/journal.pone.0188123.

86. Boi F, Minerba L, Lai ML, Marziani B, Figus B, Spanu F, et al. Both thyroid

autoimmunity and increased serum TSH are independent risk factors for malignancy in patients with thyroid nodules. J Endocrinol Invest. 2013;36:313-320. doi:103275/8579.

87. Su X, He C, Ma J, Tang T, Zhang X, Ye Z, et al. RET/PTC Rearrangements are associated with elevated postoperative TSH levels and multifocal lesions in papillary thyroid cancer without concomitant thyroid benign disease. PLoS ONE. 2016;11:e016559 6. doi:10.1371/journal.pone.0165596.

88. Landskron G, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic inflammation and cytokines in the tumour microenvironment. J Immunol Res. 2014;2014 :149185. doi:10.1155/2014/149185.

89. Karavanaki K, Karayianni C, Vassiliou I, Tzanela M, Sdogou T, Kakleas K, et al. Multiple autoimmunity, type 1 diabetes (T1DM), autoimmune thyroiditis and thyroid cancer: is there an association? A case report and literature review. J Pediatr Endocrinol Metab. 2014;27:1011-1016. doi:10.1515/jpe m-2013-0370.

90. Mussa A, Matarazzo P, Corrias A. Papillary thyroid cancer and autoimmune polyglandular syndrome. J Pediatr Endocrinol Metab. 2015; 28:793-795. doi:10.1515/jpem-2014-0268.