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Review Article

A Review on Hashimoto's Thyroiditis

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Abstract

Hashimoto's thyroiditis (HT) is an autoimmune thyroid disorder first described by Japanese physician Haraku Hashimoto in 1912 characterized by lymphocytic infiltration of the thyroid parenchyma and is influenced by immune system instability. The onset of autoimmunity may be influenced by innate and acquired immune responses. Thyroid autoantibodies (TAbs) are the primary biochemical feature. Epidemiological studies show AITD (autoimmune thyroid disease) risk is higher in women and is age-related. Risk factors include high iodine consumption, selenium insufficiency, infectious disorders, and specific medications. Genetic predisposition and environmental factors also contribute to HT. Pregnancy and sex steroids play a role in the development of autoimmune thyroiditis, with older women being more susceptible. The immune system is modified during pregnancy, with progesterone playing a significant role. About 20% of postpartum thyroiditis patients eventually develop HT. The symptoms include dysphonia, dyspnea, and dysphagia, with primary hypothyroidism causing greater systemic symptoms. Diagnosis involves circulating thyroid-specific antibodies, ultrasound examination, increased thyroid stimulating hormone, and normal serum thyroid hormone levels. Ultrasonography is crucial for diagnosing Hashimoto's thyroiditis, distinguishing it from other thyroid disorders like Graves' disease (GD). The treatment comprises levothyroxine, which effectively lowers thyroid volume, as well as vitamin D deficiency and replacement. Autoimmune thyroiditis (AIT) surgery has traditionally been reserved for people who have discomfort or compressive symptoms from goitre or co-existing malignant thyroid nodules. Thyroidectomy has lately been advocated as a treatment option for decreasing TPOAbs, as the presence of such antibodies is linked to a worse quality of life even in euthyroid patients.

Keywords: Hashimoto's thyroiditis (HT), Autoimmune thyroid disease (AITD), Autoimmune thyroiditis (AIT) Vitamin D , Levothyroxine

Introduction

HT was first described by a Japanese physician, Haraku Hashimoto, in 1912 an autoimmune disease of thyroid, first described by Hakaru Hashimoto (1912), a surgeon in Fokouka and he stated that thyroid histologic investigation revealed characteristics that were entirely distinct from the typical colloid goitre.

Hashimoto proposed the term "struma lymphamatosa" (lymphomatous goitre) [1] and claimed that this illness differs from Riedel thyroiditis (RT) and Grave disease (GD). [2] Autoimmune thyroid disorders (AITD) are brought on by immune system instability that results in an immunological attack on the thyroid. Graves' disease (GD) and Hashimoto's thyroiditis (HT), both of which are characterized by lymphocytic infiltration of the thyroid parenchyma, are the two primary clinical manifestations of the AITD. Thyrotoxicosis and hypothyroidism are the clinical signs of GD and HT [3]. The onset of autoimmunity may be influenced by the activation of innate and acquired immune responses, which can be brought on by an infection, an inflammatory reaction, or tissue damage. These findings imply that sterile thyroid damage alone, without the presence of infection, may be sufficient to cause thyroid dysfunction. Thyroid autoantibodies (TAbs), which are directed against the two main thyroid antigens thyroid peroxidase (TPO) and thyroglobulin (Tg), are the primary biochemical feature[4]. Doppler sonography or ultrasonography is a helpful method for identifying concurrent cases of Hashimoto's thyroiditis[5] Thyroid ultrasonography has been found to be a useful diagnostic tool in research between Hashimoto's thyroiditis and other conditions such vitamin D insufficiency[6]. The research revealed that levothyroxine therapy efficiently lowers thyroid volume, particularly in hypothyroid kids and adults with goitre brought on by AIT. Future study is required, although it is advised for both euthyroid and hypothyroid children with AIT. [7]

Epidemiology:

According to the epidemiological studies AIT risk is higher in women than in men, hypothyroidism caused by AIT is age-related; and the mean incidence and prevalence of spontaneous hypothyroidism as a result of AIT were 3.5–5/1000 in women (mean age 57 years) and, 0.6–1/1000 in men. [8]

Risk:

The collapse of immunological tolerance, which leads to an autoimmune attack on the thyroid itself, is assumed to be the

root cause of HT. This breakdown is thought to be a result of a combination of hereditary predisposition and environmental risk factors.

The onset of autoimmune thyroiditis is associated with high iodine consumption, selenium insufficiency, pollutants like tobacco smoke, infectious disorders such chronic hepatitis C, and specific medications. [10]

Genetic predisposition:

Tg gene is found on chromosome 8q24, and there is a link between this area and HT and autoimmune thyroid disease. [(11)] Following precise mapping of this region, the Tg gene was discovered to be one of the primary thyroid specific susceptibility genes, connected and associated with autoimmune thyroid disease.[12]

Diet:

An excessive iodine intake is linked with a higher AIT prevalence. [13]

Low selenium levels in the body may associated with immune dysfunction, a reduced selenium consumption is considered as one of the risk factor for AITD development.[14]

Another dietary component that may play a role in HT is vitamin D, whose serum levels are linked to sun exposure. Although Lower serum levels of vitamin D were seen in HT subjects. May be linked to metabolic abnormalities in hypothyroidism, particularly because thyroid dysfunction is negatively associated to vitamin deficiency severity. [15]

The role of smoking and alcohol in the etiopathogenesis of HT is still debated, and no convincing data is known so far, though it appears that moderate alcohol use may be protective against HT.[16,17]

Pregnancy and sex steroids:

Women are more likely to develop AIT than men, sex steroids play a pathogenetic role in the condition. The presence or absence of oestrogen, however, presumably has little bearing because older women may be more susceptible to HT than younger women.

Several mechanisms modify the immune system during pregnancy. The maternal fetal interface serves as a local locus of immunological advantage due to these elements together [18] Additionally, progesterone has a significant function in modulating the immune system after being released by the placenta and about 20% of postpartum thyroiditis patients eventually develop the characteristic HT. [19]

Drugs:

Women who already have high AbTPO levels appear to be at risk of hypothyroidism, and IFN-alpha therapy may cause the beginning of AIT. It may be toxic to thyroid cells or elicit immunological reactions that are harmful, leading to autoimmune hypothyroidism. [20]

Symptomology:

HT is distinguished by local and systemic symptoms such as dysphonia, dyspnea, and dysphagia [(2)]. Primary hypothyroidism, which occurs virtually invariably in HT and affects most organs and tissues with significant variability, causes greater systemic symptoms. Painless thyroiditis, painful thyroiditis, postpartum thyroiditis, and Hashimoto's encephalopathy are among the clinical variants identified.

Painless thyroiditis is so termed because the patient experiences no neck pain, and its principal feature is a transitory episode of hypothyroidism that returns to euthyroidism. [21]

The name Painful Thyroiditis refers to the progressive, intense, and painful nature of the condition unbearable discomfort in one or both lobes of the thyroid. [22]

An important clinical variation is Hashimoto's encephalopathy, which manifests as subacute cognitive decline, myoclonus, behavioural abnormalities, and seizures. [23]

Diagnosis

AIT diagnosis is determined by various factors including circulating thyroid-specific antibodies, ultrasound examination of hypo echogenic and heterogeneous gland parenchyma, increased thyroid stimulating hormone, and normal or low serum thyroid hormone levels. [24]

The diagnosis of euthyroid HT is based on the presence of TPO Abs and / or typical sonographic appearance of the thyroid gland but normal serum TSH and T4 levels.

Ultrasonography is crucial for diagnosing Hashimoto's thyroiditis, distinguishing it from other thyroid disorders like Graves' disease. Combining ultrasonography with colour flow Doppler sonography can help study differential diagnosis between Hashimoto's thyroiditis and thyroid cancer. [5]

ARFI (Acoustic radiation force impulse) is a technology that can provide quantitative elasticity measurements for differential diagnosis of malignant and benign thyroid nodules, independent of chronic autoimmune thyroiditis, and without affecting the thyroid's stiffness. [25]

Pathophysiology

HT pathogenesis is linked to autoantibodies and lymphocytic infiltrates, including B and T cells in thyroid tissue. B cell dysfunction and T cell dysfunction disrupt immune homeostasis suggesting that cellular and humoral immunity play a key role in the pathogenesis of HT. [26,27]

Cellular immunity

CD8+ T lymphocytes are detected in autoimmune thyroiditis (HT) against thyroglobulin and TPO, although only a small percentage (2-3%) are specific to thyroid antigens [(28)]. Cell death in HT is caused by both cytotoxicity and apoptotic mechanisms [29]. A population-specific CD8+ cell, known as "Suppressor T cells," can suppress damaging immune responses [30]. T regulator cells (Treg) function in T suppressor cells by reducing immunological responses via cytokine synthesis [31]. Recent research has highlighted on the involvement of Treg cells in HT, with Helios and PD-1 being key regulators of Treg cell peripheral tolerance and autoimmunity.[32, 33]

Humoral immunity

Humoral immunity is an important characteristic of thyroid disease (HT), with most patients expressing specific autoantibodies for thyroid and thyroid protein (TPO) [34]. Increased serum levels of Th1 cells, IL-17, IL-22, and IL-12 cytokines can all have an effect on HT. [35, 36] Circulating exosomes contribute to the pathophysiology of HT by influencing biological activity and generating antigen presentation, inflammatory activation, autoimmune diseases, and tumour metastasis. HT is frequently accompanied with other autoimmune illnesses, implying a probable poly-autoimmune aetiology .[37]

Recently, a variant of HT called IG4 thyroiditis has been identified and is part of a systemic autoimmune disease characterized by the presence of IG4-positive cells. [38]

Follicular helper T - cells

Follicular helper T cells (Tfh) are a newly identified subset of T helper cells involved in promoting antigen-specific B cells through IL-21 production [39] they express CXCR5 and ICOS protein, and have been found in thyroid tissue of HT patients, indicating their involvement in disease pathogenesis. [40]

DNA fragments and micro RNA

In vitro thyroid cell damage and genomic DNA release can result in an inflammatory response and impaired thyroid protein activity [41]. Histone H2B, when attached to genomic DNA, activates innate immunity, resulting in thyroid autoimmunity, implying that sterile thyroid damage triggers immunity. [42]

MicroRNAs (miRNA), which are tiny noncoding RNA sections, have also been linked to thyroid immunity pathogenesis. Several miRNAs have been found to regulate innate and adaptive immune responses .[43]

Treatment:

The study found that levothyroxine treatment effectively reduces thyroid volume, especially in hypothyroid children and adolescents with goitre due to AIT. It is recommended for both euthyroid and hypothyroid children with AIT, though future research is needed. [7]

The amount of LT4 needed to normalise serum TSH is determined by the amount of residual endogenous thyroid function present as well as the patient's weight, particularly lean body mass. [44] The thyroid gland is estimated to produce 85 to 100 mcg of T4 per day and 5 to 6.5 mcg of T3 per 24 hours, with the remaining daily production of 26.5 mcg/day of T3 resulting from peripheral conversion of T4 to T3 by type 1 and type 2 deiodinases in patients with a preserved degree of endogenous thyroid function. [(45]

According to NHANES III(third national health and nutrition examination survey) data, the median TSH for adults aged 30-39 years is 1.2 mIU/ml, with the 2.5 and 97.5 percentiles ranging from 0.42 to 3.56 mIU/ml, respectively. TSH levels of 4-6 mIU/ml may be appropriate for older people. The best period for making judgements on LT4 dose adjustments is 6-8 weeks after starting therapy or changing the dose, to provide enough time for the hypothalamus-pituitary-thyroid axis set point to be re-established. [46]

The significance of glucocorticoids has been called into doubt, as they may regulate thyroiditis and acutely improve thyroid function, despite the hazards associated with high doses and long therapy.Outweigh the[47]. Advantage However, prednisolone can be used for a brief period of time in IG-4 disease patients. [48]

As several selenoproteins are involved in thyroid function, selenium plays an important role in human thyroid hormone homeostasis[(49)] Oral administration of selenium in the form of seleno-methionine would be beneficial in HT patients with selenium deficiency and should protect the thyroid gland from the autoimmune reaction.[50]

When clinically indicated, patients with HT may benefit from screening for vitamin D deficiency and supplementation [51], as well as monthly monitoring of calcium and 25[OH] D levels if necessary. The levels of AbTPO and AbTg significantly decreased following six months of vitamin D administration. [52, 53]

Surgery:

Surgery for HT has typically been reserved for individuals who come with pain or compressive symptoms related to goitre or co-existing malignant thyroid nodules.[54] Thyroidectomy, however, has lately been proposed as a therapeutic approach for lowering TPOAbs , as the existence of such antibodies is associated with a worse quality of life even in euthyroid patients. [55]

Thyroidectomy may result in problems. Hypocalcemia, wound infection, hematoma, recurrent laryngeal nerve (RLN) damage, and Horner's syndrome are the most common postoperative sequelae. [56]

Hypocalcemia is a significant postoperative complication of thyroid surgery that can cause severe symptoms and lengthen hospitalisation.[57]

Dietary modifications:

Dietary changes are a non-invasive strategy that can give quantitative results. To minimise thyroid inflammation, anti-inflammatory substances such as vitamin D, antioxidants, monounsaturated and polyunsaturated fatty acids, magnesium, and zinc are essential. Thyroid hormone synthesis and metabolism are aided by iodine and selenium. Because of the high prevalence of anaemia and cardiovascular illness in this group of Hashimoto's thyroiditis patients, an adequate intake of iron, folic acid, and vitamin B12 is also essential. Gluten and lactose should be avoided in the presence of food intolerances or disorders such as celiac disease, according to recent research. One of the fundamentals of a well-balanced diet is to restrict pro-inflammatory foods such as saturated fats, sweets, and refined carbs.[58]

Conclusion:

Hashimoto's thyroiditis (HT) is an autoimmune condition characterized by the infiltration of lymphocytes into the thyroid tissue, resulting in hypothyroidism. The onset of HT is influenced by genetic factors, environmental triggers, and hormonal changes, particularly in women.

Crucial diagnostic tools such as ultrasonography and specific antibodies aid in identifying HT. The pathophysiology involves both cellular and humoral immunity, with significant roles played by CD8+ T lymphocytes, B cells, and follicular helper T cells. The complexity of HT is contributed to by genetic elements, environmental factors, and dietary components.

Treatment options encompass levothyroxine therapy, adjusted based on the patient's weight and remaining thyroid function. Additionally, benefits may arise from selenium supplementation and vitamin D administration. Surgery, usually reserved for symptomatic cases, could be considered to enhance quality of life.

Dietary adjustments, emphasizing anti-inflammatory substances and avoiding pro-inflammatory foods, can complement HT management. Regular monitoring, especially during pregnancy and hormone therapy, is crucial. In essence, a comprehensive approach, taking into account genetic, environmental, and lifestyle factors, is essential for comprehending and addressing Hashimoto's thyroiditis.

References:

1. Hashimoto, H. (1912) Zora Kenntniss der lymphoatosen Veranderung der Schilddrüse (Struma lymphomatoa). Langenbecks archiv fur klinische chirurgie, 97, 219-248. World Journal of Neuroscience, Vol.7 No.3,2017

2. Ralli M, Angeletti D, Fiore M, D'Aguanno V, Lambiase A, Artico M, de Vincentiis M, Greco A. Hashimoto's thyroiditis: An update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. Autoimmun Rev [Internet]. 2020 Oct;19(10):102649. https://doi.org/10.1016/j.autrev.2020.102649 PMid:32805423

3. Ahmed R, Al-Shaikh S, Akhtar M. Hashimoto thyroiditis: a century later. Advances in anatomic pathology [internet]. 2012 May 1;19(3):181-6 https://doi.org/10.1097/PAP.0b013e3182534868 PMid:22498583

4. Zaletel K, Gaberscek S. Hashimoto's thyroiditis: from genes to the disease. Current genomics [internet]. 2011 Dec 1;12(8):576-88. https://doi.org/10.2174/138920211798120763 PMid:22654557 PMCid:PMC3271310

5. Wu G, Zou D, Cai H, Liu Y. Ultrasonography in the diagnosis of Hashimoto's thyroiditis. Frontiers in Bioscience-Landmark [internet]. 2016 Jun 1;21(5):1006-12. https://doi.org/10.2741/4437 PMid:27100487

6. Bozkurt NC, Karbek B, Ucan B, Sahin M, Cakal E, Ozbek M, Delibasi T. The association between severity of vitamin D deficiency and Hashimoto's thyroiditis. Endocrine Practice. [internet] 2013 May 1;19(3):479-84. https://doi.org/10.4158/EP12376.OR PMid:23337162

7. Svensson J, Ericsson UB, Nilsson P, Olsson C, Jonsson B, Lindberg B, Ivarsson SA. Levothyroxine treatment reduces thyroid size in children and adolescents with chronic autoimmune thyroiditis. The Journal of Clinical Endocrinology & Metabolism [internet]. 2006 May 1;91(5):1729-34. https://doi.org/10.1210/jc.2005-2400 PMid:16507633

8. Ragusa F, Fallahi P, Elia G, Gonnella D, Paparo SR, Giusti C, Churilov LP, Ferrari SM, Antonelli A. Hashimotos' thyroiditis: Epidemiology, pathogenesis, clinic and therapy. Best Practice & Research Clinical Endocrinology & Metabolism [internet] 2019 Dec 1;33(6):101367. https://doi.org/10.1016/j.beem.2019.101367 PMid:31812326

9. Chistiakov DA. Immunogenetics of Hashimoto's thyroiditis. Journal of autoimmune diseases [Internet] 2005 Dec;2(1):1-21. https://doi.org/10.1186/1740-2557-2-1 PMid:15762980 PMCid:PMC555850

10. Duntas LH. Environmental factors and autoimmune thyroiditis. Nature clinical practice Endocrinology & metabolism [internet] 2008 Aug;4(8):454-60. https://doi.org/10.1038/ncpendmet0896

11. Tomer Y, Ban Y, Concepcion E, Barbesino G, Villanueva R, Greenberg DA, Davies TF. Common and unique susceptibility loci in Graves and Hashimoto diseases: results of whole-genome screening in a data set of 102 multiplex families. The American Journal of Human Genetics. 2003 Oct 1;73(4):736-47. https://doi.org/10.1086/378588 PMid:12973666 PMCid:PMC1180598

12. Tomer Y, Greenberg DA, Concepcion E, Ban Y, Davies TF. Thyroglobulin is a thyroid specific gene for the familial autoimmune thyroid diseases. The Journal of Clinical Endocrinology & Metabolism. 2002 Jan 1;87(1):404-07 https://doi.org/10.1210/jcem.87.1.8291 PMid:11788684

13. Iddah MA, Macharia BN. Autoimmune thyroid disorders. International Scholarly Research Notices. 2013;2013;509764 https://doi.org/10.1155/2013/509764 PMid:23878745 PMCid:PMC3710642

14. Duntas LH. Selenium and the thyroid: a close-knit connection. The Journal of Clinical Endocrinology & Metabolism. 2010 Dec 1;95(12):5180-8. https://doi.org/10.1210/jc.2010-0191 PMid:20810577

15. Tamer G, Arik S, Tamer I, Coksert D. Relative vitamin D insufficiency in Hashimoto's thyroiditis. Thyroid. 2011 Aug 1;21(8):891-6. https://doi.org/10.1089/thy.2009.0200 PMid:21751884

16. Carlé A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, Jørgensen T, Laurberg P. Moderate alcohol consumption may protect against overt autoimmune hypothyroidism: a population-based case-control study. European journal of endocrinology. 2012 Oct 1;167(4):483-90. https://doi.org/10.1530/EJE-12-0356 PMid:22802427

17. Effraimidis G, Tijssen JG, Wiersinga WM. Alcohol consumption as a risk factor for autoimmune thyroid disease: a prospective study. European thyroid journal. 2012 Jul 1;1(2):99-104. https://doi.org/10.1159/000338920 PMid:24783003 PMCid:PMC3821464

18. Yin X, Latif R, Tomer Y, Davies TF. Thyroid epigenetics:X chromosome inactivation in patients with autoimmune thyroid disease. Annals of the New York Academy of Sciences 2007 Sep;1110(1): 193-200. https://doi.org/10.1196/annals.1423.021 PMid:17911434

19. Davies TF. The thyroid immunology of the postpartum period. Thyroid 1999 Jul;9(7): 675-84 https://doi.org/10.1089/thy.1999.9.675 PMid:10447014

20. Tomer Y, Menconi F. Interferon induced thyroiditis. Best practice & research. Clinical endocrinology & metabolism 2009 Dec;23(6): 703-12. https://doi.org/10.1016/j.beem.2009.07.004 PMid:19942147 PMCid:PMC2818066

21. AMINO N, TADA H, HIDAKA Y. Postpartum autoimmune thyroid syndrome: a model of aggravation of autoimmune disease. Thyroid 1999 Jul;9(7):705-13. https://doi.org/10.1089/thy.1999.9.705 PMid:10447018

22. Peng CC, Huai-En Chang R, Pennant M, Huang HK, Munir KM. A literature review of painful Hashimoto thyroiditis: 70 published cases in the past 70 years. Journal of the Endocrine Society. 2020 Feb;4(2):bvz008. https://doi.org/10.1210/jendso/bvz008 PMid:32047869 PMCid:PMC7003982

23. Pinedo-Torres I, Paz-Ibarra JL. Current knowledge on Hashimoto's encephalopathy:a literature review. Medwave 2018 Oct 18;18(06). https://doi.org/10.5867/medwave.2018.06.7298 PMid:30451215

24. Ragusa F, Fallahi P, Elia G, Gonnella D, Paparo SR, Giusti C, Churilov LP, Ferrari SM, Antonelli A. Hashimotos' thyroiditis: Epidemiology, pathogenesis, clinic and therapy. Best Practice & Research Clinical Endocrinology & Metabolism. [internet] 2019 Dec 1;33(6):101367. https://doi.org/10.1016/j.beem.2019.101367 PMid:31812326

25. Han R, Li F, Wang Y, Ying Z, Zhang Y. Virtual touch tissue quantification (VTQ) in the diagnosis of thyroid nodules with coexistent chronic autoimmune Hashimoto's thyroiditis: A preliminary study. European Journal of Radiology [Internet]. 2015 Feb 1;84(2):327-31. https://doi.org/10.1016/j.ejrad.2014.11.005 PMid:25481824

26. McLachlan SM, Rapoport B. Breaking tolerance to thyroid antigens: changing concepts in thyroid autoimmunity. Endocrine reviews. 2014 Feb 1;35(1):59-105. https://doi.org/10.1210/er.2013-1055 PMid:24091783 PMCid:PMC3895862

27. Smith TJ, Hegedüs L. Graves' disease. New England Journal of Medicine. 2016 Oct 20;375(16):1552-65. https://doi.org/10.1056/NEJMra1510030 PMid:27797318

28. Ehlers M, Thiel A, Bernecker C, Porwol D, Papewalis C, Willenberg HS, Schinner S, Hautzel H, Scherbaum WA, Schott M. Evidence of a combined cytotoxic thyroglobulin and thyroperoxidase epitope-specific cellular immunity in Hashimoto's thyroiditis. The Journal of Clinical Endocrinology & Metabolism. 2012 Apr 1;97(4):1347-54. https://doi.org/10.1210/jc.2011-2178 PMid:22259066

29. Kotani T, Aratake Y, Hirai K, Fukazawa Y, Sato H, Ohtaki S. Apoptosis in thyroid tissue from patients with Hashimoto's thyroiditis. Autoimmunity. 1995 Jan 1;20(4):231-6. https://doi.org/10.3109/08916939508995700 PMid:7578885

30. Roldán JC, Amaya-Amaya J, Castellanos-De La Hoz J, Giraldo-Villamil J, Montoya-Ortiz G, Cruz-Tapias P, Rojas-Villarraga A, Mantilla RD, Anaya JM. Autoimmune thyroid disease in rheumatoid arthritis: a global perspective. Arthritis. 2012;2012. https://doi.org/10.1155/2012/864907 PMid:23209899 PMCid:PMC3505628

31. MacDonald TT. Suppressor T cells, rebranded as regulatory T cells, emerge from the wilderness bearing surface markers. Gut. 2002 Sep 1;51(3):311-2. https://doi.org/10.1136/gut.51.3.311 PMid:12171947 PMCid:PMC1773337

32. Shevach EM. Suppressor T cells: rebirth, function and homeostasis.Current Biology. 2000 Aug 1;10(15):R572-5. https://doi.org/10.1016/S0960-9822(00)00617-5 PMid:10959833

33. Hu Y, Zhang L, Chen H, Liu X, Zheng X, Shi H, Jiang L, Cui D. Analysis of regulatory T cell subsets and their expression of helios and PD-1 in patients with Hashimoto thyroiditis. International Journal of Endocrinology. 2019 May 13;2019. https://doi.org/10.1155/2019/5368473 PMid:31214258 PMCid:PMC6535823

34. Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ, O'Leary P. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. The Journal of Clinical Endocrinology & Metabolism. 2010 Mar 1;95(3):1095-104. https://doi.org/10.1210/jc.2009-1977 PMid:20097710

35. Ajjan RA, Weetman AP. Cytokines in thyroid autoimmunity. Autoimmunity 2003;36:351-9. https://doi.org/10.1080/08916930310001603046 PMid:14669942

36. Trifari S, Kaplan CD, Tran EH, Crellin NK, Spits H. Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from TH-17, TH1 and TH2 cells. Nature immunology. 2009 Aug;10(8):864-71. https://doi.org/10.1038/ni.1770 PMid:19578368

37. Figueroa-Vega N, Alfonso-Perez M, Benedicto I, Sanchez-Madrid F, Gonzalez-Amaro R, Marazuela M. Increased circulating pro-inflammatory cytokines and Th17 lymphocytes in Hashimoto's thyroiditis. The Journal of Clinical Endocrinology & Metabolism. 2010 Feb 1;95(2):953-62. https://doi.org/10.1210/jc.2009-1719 PMid:20016049

38. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K. High serum IgG4 concentrations in patients with sclerosing pancreatitis. New England Journal of Medicine. 2001 Mar 8;344(10):732-8. https://doi.org/10.1056/NEJM200103083441005 PMid:11236777

39. Spolski R, Leonard WJ. IL-21 and T follicular helper cells.International immunology 2010 Jan 1; 22(1): 7-12 https://doi.org/10.1093/intimm/dxp112 PMid:19933709 PMCid:PMC2795365

40. Zhu C, Ma J, Liu Y, Tong J, Tian J, Chen J, Tang X, Xu H, Lu L, Wang S. Increased frequency of follicular helper T cells in patients with autoimmune thyroid disease: The Journal of Clinical Endocrinology & Metabolism. 2012; 97: 943-50 https://doi.org/10.1210/jc.2011-2003 PMid:22188745

41. Kono H, Rock KL. How dying cells alert the immune system to danger. Nature Reviews Immunology. 2008 Apr;8(4):279-89. https://doi.org/10.1038/nri2215 PMid:18340345 PMCid:PMC2763408

42. Ishii KJ, Suzuki K, Coban C, Takeshita F, Itoh Y, Matoba H, Kohn LD, Klinman DM. Genomic DNA released by dying cells induces the maturation of APCs. The Journal of Immunology. 2001 Sep 1;167(5):2602-7. https://doi.org/10.4049/jimmunol.167.5.2602 PMid:11509601

43. Xiao C, Rajewsky K. MicroRNA control in the immune system: basic principles. Cell 2009; 136: 26-36 https://doi.org/10.1016/j.cell.2008.12.027 PMid:19135886

44. Klubo-Gwiezdzinska J, Wartofsky L. Hashimoto thyroiditis: An evidence-based guide: Etiology, diagnosis and treatment. Pol. Arch. Intern. Med [internet].2022 Mar 3;132:16222. https://doi.org/10.20452/pamw.16222 PMid:35243857 PMCid:PMC9478900

45. Pilo AL, Iervasi GI, Vitek FR, Ferdeghini MA, Cazzuola FR, Bianchi RO. Thyroidal and peripheral production of 3, 5, 3'-triiodothyronine in humans by multicompartmental analysis. American Journal of Physiology-Endocrinology and Metabolism. 1990 Apr 1;258(4):E715-26. https://doi.org/10.1152/ajpendo.1990.258.4.E715 PMid:2333963

46. Hollowell JG, Staehling NW, Flanders WD,Hannon WH,Gunter EW,spencer CA,Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III).The Journal of clinical Endocrinology & Metabolism. 2002; 87: 489-499 https://doi.org/10.1210/jcem.87.2.8182 PMid:11836274

47. Topliss DJ. Clinical update in aspects of the management of autoimmune thyroid diseases. Endocrinology and Metabolism. 2016 Dec 1;31(4):493-9. https://doi.org/10.3803/EnM.2016.31.4.493 PMid:28029020 PMCid:PMC5195823

48. Watanabe T, Maruyama M, Ito T, Fujinaga Y, Ozaki Y, Maruyama M, Kodama R, Muraki T, Hamano H, Arakura N, Kadoya M. Clinical features of a new disease concept, IgG4-related thyroiditis. Scandinavian journal of rheumatology. 2013 Aug 1;42(4):325-30. https://doi.org/10.3109/03009742.2012.761281 PMid:23496326

49. Brown KM, Arthur JR. Selenium, selenoproteins and human health: a review. Public health nutrition. 2001 Apr;4(2b):593-9 https://doi.org/10.1079/PHN2001143 PMid:11683552

50. Köhrle J. Selenium and the thyroid. Current Opinion in Endocrinology, Diabetes and Obesity. 2013 Oct 1;20(5):441-8. https://doi.org/10.1097/01.med.0000433066.24541.88 PMid:23974773

51. Liontiris MI, Mazokopakis EE. A concise review of Hashimoto thyroiditis (HT) and the importance of iodine, selenium, vitamin D and gluten on the autoimmunity and dietary management of HT patients. Points that need more investigation. Hell J Nucl Med 2017;20:51-6.

52. Roehlen N, Doering C, Hansmann ML, Gruenwald F, Vorlaender C, Bechstein WO,Holzer K, Badenhoop K, Penna-Martinez M. Vitamin D, FOXO3a, and Sirtuin1 in hashimoto's thyroiditis and differentiated thyroid cancer. Frontiers in Endocrinology. 2018 Sep 11;9:527. https://doi.org/10.3389/fendo.2018.00527 PMid:30271381 PMCid:PMC6142903

53. Chao G, Zhu Y, Fang L. Correlation Between Hashimoto's Thyroiditis-Related Thyroid Hormone Levels and 25-Hydroxyvitamin D. Frontiers in Endocrinology. 2020 Feb 14;11:4. https://doi.org/10.3389/fendo.2020.00004 PMid:32117049 PMCid:PMC7034299

54. Gan T, Randle RW. The role of surgery in autoimmune conditions of the thyroid. Surgical Clinics. 2019 Aug 1;99(4):633-48. https://doi.org/10.1016/j.suc.2019.04.005 PMid:31255196

55. Mack LA, Pasieka JL. An evidence-based approach to the treatment of thyroid lymphoma. World J Surg. [internet] 2007 May;31(5):978-86. https://doi.org/10.1007/s00268-005-0768-z PMid:17235456

56. Chahardahmasumi E, Salehidoost R, Amini M, Aminorroaya A, Rezvanian H, Kachooei A, Iraj B, Nazem M, Kolahdoozan M. Assessment of the early and late complication after thyroidectomy. Advanced biomedical research [Internet]. 2019;8. https://doi.org/10.4103/abr.abr_3_19 PMid:30993084 PMCid:PMC6425745

57. Bourrel C, Uzzan B, Tison P, Despreaux G, Frachet B, Modigliani E, Perret GY. Transient hypocalcemia after thyroidectomy. Annals of Otology, Rhinology & Laryngology. 1993 Jul;102(7):496-501. https://doi.org/10.1177/000348949310200702 PMid:8333670

58. Osowiecka K, Myszkowska-Ryciak J. The Influence of Nutritional Intervention in the Treatment of Hashimoto's Thyroiditis-A Systematic Review. Nutrients [Internet]. 2023 Feb 20;15(4):1041. https://doi.org/10.3390/nu15041041 PMid:36839399 PMCid:PMC9962371