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Hashimoto's Disease: Associated Thyroid Gland Disorders, Pharmacological, and Nutritional Interventions

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Abstract

Hashimoto's disease is a condition that occurs when an affected person's immune system attacks their thyroid gland and produces an immune response that results in low levels of thyroid hormones in the blood. These hormones are important in maintaining the body's metabolic processes and the lack of thyroid hormones causes the symptoms of Hashimoto's disease that include weight gain, paleness, coldness, birth defect, infertility, menorrhagia, and even death in rare cases of uncontrolled hypothyroidism. The disease requires a blood test to determine the levels of circulating thyroid hormones in the blood or the presence of specific antibodies. Thyroid hormone replacement is used to raise the levels of thyroid hormones in the body, if the hormone test shows that they are deficient. People who are middle aged, female, and have or are predisposed to an autoimmune disorder are most at risk for developing the disease. In recent times, the notion that the antidote for managing Hashimoto's disease may be found in common food and supplements has grown among endocrinologists and caregivers. This review is intended to investigate the various aspects of the disease that include its pathogenesis, associated disorders, pharmacological and nutritional interventions.

Keywords

Hashimoto, Autoimmune, Hypothyroidism, Thyroid, Antibodies, Pharmacological

1. Introduction

Hashimoto's disease is an autoimmune disorder that affects the thyroid gland. The condition can also be referred to as Hashimoto's thyroiditis or chronic lym-

phocytic thyroiditis. The frame diagram (**Figure 1**) [1] is designed to ease understanding for the readers. The disease was first described in 1912, by its namesake Hakaru Hashimoto [2]. Due to the disease, an affected person's immune system will target their thyroid gland and cause it to not function properly [3]. In other words, antibodies are made against the affected person's own thyroid gland, leading to hypothyroidism. Hashimoto's is the most common cause of hypothyroidism in the United States of America (USA). The thyroid gland is in the neck, and it is butterfly-shaped in appearance (**Figure 2**). The thyroid gland produces two hormones in the follicular cells: triiodothyronine (T3) and tetraiodothyronine (thyroxine - T4) [4]. While the parafollicular cells produce a third thyroid hormone called calcitonin, its production is not impacted by Hashimoto's. In Hashimoto's disease, it is the follicular cells of the thyroid glands that are destroyed. While being like Hashimoto's disease, the thyroid gland can also be affected by other disorders like goiter, hypothyroidism, hyperthyroidism, Graves' disease, thyroid, nodules, and thyroid cancer.

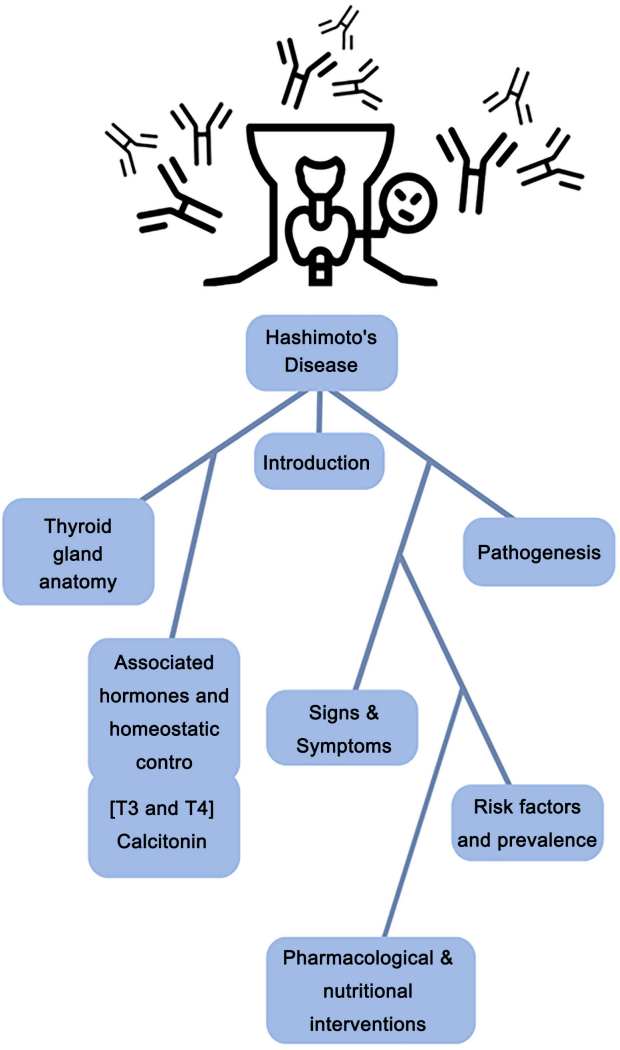


Figure 1. Hashimoto's disease—A frame diagram [1].

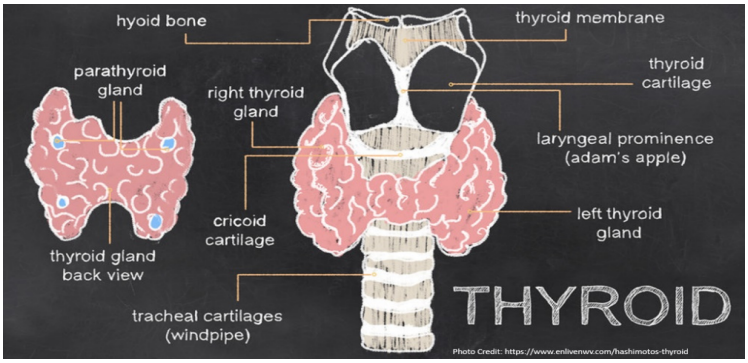


Figure 2. Showing anatomical location of the thyroid gland (the blue spots on the thyroid gland are the parathyroid glands). Photo Credit: https://enliverwv.com/flashnotes.thyroid [5].

1.1. Objectives and Design

This review is intended to investigate the various aspects of the disease that include thyroid gland anatomy and the homeostatic control of the associated hormones, associated disorders, its pathogenesis, risk factors and prevalence, signs and symptoms, effects on the body, pharmacological and nutritional interventions. Although the topic of Hashimoto's disease has been widely reviewed, this article is designed to research composite information about the disease. In other words, there hasn't been any available review article that has encompassed various aspects of the disease in a single paper as ours.

1.2. Methods

Sources of information for this article included PubMed, Published Textbooks on Endocrinology, LDNscience - MedInsight Research Institute, Scopus, ISI Web of Science, Google Scholar Short Essays on Medical topics up to 2022. Images were retrieved from other published articles and online.

1.3. Limitation(s)

Although the article researched on the efficacy of the pharmacological intervention on pregnant and teens demographic groups, no literature is available on pre-teens. Therefore, this research is silent on the probability that Hashimoto's disease could have an early onset in pre-teens. Also, there hasn't been any clinical trial on the efficacy of the various food supplements that have been speculated to ameliorate the Hashimoto's disease in patients.

2. Signs and Symptoms

According to National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [6], Hashimoto's disease affects the thyroid gland by destroying the follicular cells, which causes chronic damage to the thyroid gland. This then affects the secretion of hormones produced by the thyroid gland (follicular cells related hormones only), which causes the onset of its symptoms. One of the first signs of Hashimoto's disease is the appearance of an abnormally large neck, re-

ferred to as goiter. In this case, the goiter is caused by inflammation of the thyroid gland [3]. Some of the symptoms of this disorder include cold sensitivity, dry skin, constipation, weight gain, weakness, hair loss, fatigue, brittle nails, depression, slow pulse, appearing pale, and others (LDNscience - MedInsight Research Institute, 2022) [7]. Hashimoto's symptoms checklist is shown in **Figure 3** [8].

Effects on the Body

Hashimoto's disease has several effects on the human body due to its damage to the thyroid gland and its associated hormones production. In relation to hypothyroidism, the hypothalamus releases thyrotropin releasing hormone (TRH) whenever the body detects a low quantity of circulating thyroid hormone. The anterior pituitary gland in response to TRH releases an elevated amount of thyroid stimulating hormone (TSH). This increased secretion of TSH will cause the thyroid gland to increase its hormone formation. Unfortunately, the newly synthesized thyroid hormones will be stored in the colloids of the thyroid gland and will not be released. Consequently, the thyroid gland will gradually swell in size [9]. This increase in thyroid gland size causes a notable swelling of the neck, which is referred to as goiter, leading to hypothyroidism [3] [10]. This can result in birth defects, if left untreated in pregnant women (LDNscience - MedInsight Research Institute, 2022) [7]. Another common symptom is weight gain. This occurs due to the thyroid hormones effect on the rate that a person's metabolism occurs. Metabolism affects a person's heart rate and digestion, and it refers to the breaking down and building up of chemical substances, which are catabolism and anabolism, respectively. The decrease in thyroid hormone production seen in Hashimoto's disease affects metabolism and thereby causes the symptoms of weight gain, feeling cold, paleness, and weakness with a low pulse [9] [11].

Figure 3. Hashimoto's symptoms checklist. Table Credit [8].

The development of thyroid dysfunction during pregnancy can cause both maternal and fetal complications. It has been already demonstrated that both overt and subclinical hypothyroidism are associated with obstetrical repercussions. Maternal complications include anemia, postpartum hemorrhage, Cardiac dysfunction, preeclampsia, and placental abruption; fetal complications include fetal distress, premature birth, and/or low birth weight, congenital malformations, and fetal/perinatal death [12]-[17]. High cholesterol and myxedema are also common complications [18].

3. Thyroid Regulation

The thyroid gland is regulated using a negative feedback loop. Specifically, once the thyroid gland has produced a certain quantity of the thyroid hormones, a signal will be sent to the brain and regulation will occur via the hypothalamic-pituitary axis. The hypothalamus, considered as a neuroendocrine organ, located in the brain, is responsible for the release of thyroid hormone by releasing either TRH. If TRH is released, it would go from the hypothalamus to the anterior pituitary gland and cause the release of thyroid stimulating hormone (TSH). While the "[i]nhibition of TRH secretion leads to shut-off of TSH secretion, which leads to shut-off of thyroid hormone secretion." [19]. During inhibition, the levels of TSH secreted from the pituitary gland will be decreased. Whenever the thyroid gland is not being controlled by the negative feedback loop, TRH will be secreted and cause the production and secretion of TSH into the bloodstream which would travel to the thyroid gland. When the TSH reaches the thyroid gland, it causes the production of thyroid hormones. But due to the negative feedback mechanisms, whenever the body reaches its peak amount of thyroid hormones in the blood, it will alert the hypothalamus. The hypothalamus, in turn, will cease its secretion of TRH. Due to it being a feedback loop, "[a]s thyroid hormone levels decay below the threshold, negative feedback is relieved, TRH secretion starts again, leading to TSH secretion" [19]. This means that the levels of thyroid hormone in the blood will determine if more or less of it be produced, as illustrated in **Figure 4** below.

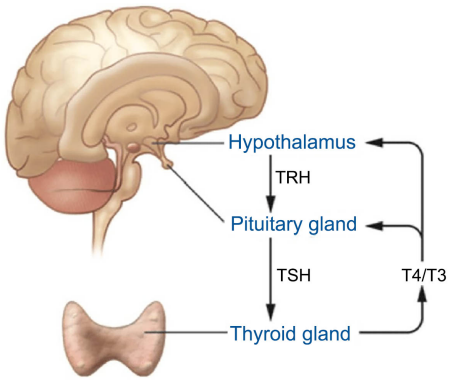


Figure 4. Thyroid hormones regulation illustration: Photo Credit [20].

There are two main hormones that are affected by Hashimoto's disease. They include the triiodothyronine or T3, and thyroxine or T4 [4]. Both hormones are secreted by the thyroid gland; however, with Hashimoto's disease, these hormones are not being released into the blood for circulation. Hashimoto's disease is an autoimmune disorder, and in most cases, the affected person's immune system produces antibodies that prevent the production of thyroid hormone. It does this by causing immune responses that result in either the destruction of the follicular cells where T3 and T4 are produced, or by producing antithyroid antibodies that block the TSH receptor of the thyroid gland that would normally cause the production and secretion of thyroid hormone [9]. When the body is functioning correctly, T3 and T4 will help to control the body's metabolism, the rate in which your body breaks down or builds up nutrients. Some of the treatments for Hashimoto's disease, which will be discussed later, may result in the removal or reduction of parts of the thyroid gland. The level of calcitonin that is secreted into the bloodstream can also be decreased along with the levels of T3 and T4 in that circumstance [9].

4. Risk Factors and Prevalence

There are some physiological risk factors that affect a person's chances of developing Hashimoto's disease. Around 14 million people (about twice the population of Arizona) are currently affected by the disease in the US alone [21]. Hashimoto' Thyroiditis commonly affects more women than men as the former is 8 times more likely to suffer. It is currently known that increasing age and female gender are associated with increasing risk of developing autoimmune disorders [22] [23]. However, it can also affect men of any age, including children [6]. Studies by the International Scholarly Research Notices, ISRN [24] indicate that this disease is prevalent in 1 - 3 percent of the world's population. There is a genetic component of inheriting Hashimoto's disease from the parents through heredity [25]. This also means that a person who is affected by the condition may pass it down to their offspring. Since this disease is impacted by the body's immune system, a person who has an autoimmune disorder may be at a higher risk for developing the condition. Autoimmune diseases such as celiac disease, lupus, rheumatoid arthritis, Sjogren's syndrome, and type 1 diabetes are risk factors [26]. Middle aged people, ages 45 to 60, are at a greater risk as well. Being exposed to radiation will increase a person's likelihood of developing the disease [27]. Removal of some or all the thyroid gland, or radiation treatment can cause hypothyroidism which would have the same symptoms as Hashimoto's. Autoimmunity is considered the second most frequent etiology of hypothyroidism [28] [29] [30] [31] [32].

There have been reports of non-thyroid autoantibodies in autoimmune thyroid disease. Weetman [23] reported that autoimmune thyroid disease is frequently accompanied by other organ-specific and non-organ specific diseases, because there is sharing of genetic and possibly environmental susceptibility factors. Weetman [23] added that these associations are well recognized in the au-

toimmune polyglandular syndromes; autoimmune thyroid disease is one of three major endocrinopathies in the type 2 syndrome and occurs in around 4% of type 1 patients. The comorbidity in Hashimoto's disease, therefore, becomes major interest in its pathophysiology and pathogenesis. It is characterized clinically by gradual thyroid failure, with or without goiter formation, due to lymphocytic infiltration and autoimmune-mediated destruction of the thyroid gland involving apoptosis of thyroid epithelial cells [2]. Although the simultaneous occurrence of a neoplasm and Hashimoto's disease (Hashimoto "thyroiditis" lymphadenoid goiter, struma lymphomatosa) in a thyroid gland has been noted infrequently, in a study by Morris *et al.* [33] that was concerned primarily with clinical aspects and pathogenesis of several types of thyroiditis, a significant statistical relation was found between malignant thyroid neoplasms and Hashimoto's disease of the thyroid gland. **Figure 5** illustrates the risk factors for thyroid cancer [34].

5. Diagnosis

Hashimoto's disease requires medical testing to determine if the thyroid hormone levels present in the person's blood are deficient [6]. There are two different tests that can be used to determine the T3 and T4 levels, these include the hormone test and the antibody test [27] A hormone test checks to see if the blood contains a low level of thyroid hormone, as well as an increased TSH level [27]. With Hashimoto's disease, the level of circulating T3 and T4 will be low, and the anterior pituitary gland will raise the levels of TSH secreted to counteract this [9] as shown in **Figure 6** [35]. The second testing option is called the antibody test, and it tests for thyroid peroxidase, used to make thyroid hormone [27].

This antibody is an immune response that blocks the TSH receptors of the thyroid gland and stops thyroid hormone production. A positive result for this antibody does not guarantee a diagnosis of Hashimoto's and doctors usually recommend having a hormone test following the development of the symptoms associated with this condition [27]. Since goiter is the most common sign associated with the condition, medical testing is usually conducted once the swelling of the neck has been noted.

6. Treatment, Pharmacological Interventions and Nutritional Therapy

The treatment for Hashimoto's disease is to manage the symptoms of the disease. When the goiter is caused by Hashimoto's, the administration of thyroid hormone into the blood will also counteract the condition, as well as taking medication that prevents TSH from being released. For hypothyroidism or low levels of T3 and T4 that may occur, hormone replacement is an option to replace the amount of thyroid hormone in the blood [4] Since T4 has a longer lifespan than T3, it is usually more common and affordable to be used as a supplement. There is also a synthetic form of thyroxine referred to as levothyroxine (LT4) that is used in thyroid hormone replacement therapies [27] Levothyroxine is an

oral treatment shown in **Figure 7(a)** [36], and it is a synthetic version of T4, while Liothyronine is the synthetic version of T3 shown in **Figure 7(b)** [37]. Since T4 has a longer half-life than T3, it can be given as an oral supplement [38].

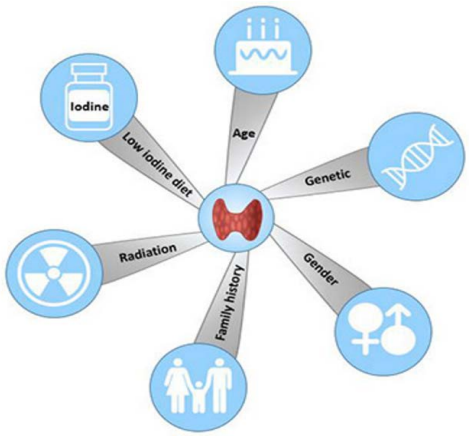
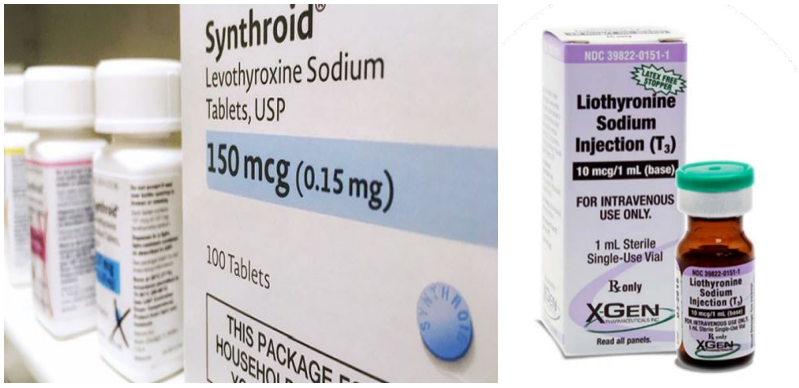


Figure 5. Risk factors for thyroid cancer illustrated [34].

Figure 6. Showing factors tested in HT. Photo Credit: [35].



(a) (b)

Figure 7. (a) Showing pharmacological agents - Levothyroxine Sodium [36]. (b) Liothyronine Sodium. [37].

and it is injectable and often more expensive than Levothyroxine [38]. The replacement of thyroid hormone allows the individuals with this condition to improve the metabolic activity in their bodies, resulting in regaining of homeostasis and stopping the symptoms caused due to metabolic changes associated with Hashimoto's disease [39]. Roberts *et al.* [40] reported in their study of population sample that treatment with Levothyroxine (LT4) had a positive effect on reducing the rates of miscarriages and premature delivery. They added that timing of treatment initiation appears to be of critical importance. Because the LT4 treatment turned out to be extremely effective in reducing the number of miscarriages when given during the preliminary stages of pregnancy as miscarriages generally occurred within the first trimester.

In addition to pharmacological interventions, some caregivers have equally found nutritional therapy and food supplements to be helpful. The food and supplements that are considered useful in the management of Hashimoto's disease are generally considered as Non-pharmacological Interventions (NPIs). Several supplements have been identified to ameliorate the Hashimoto's thyroiditis (HT) that include Zinc, Magnesium, Curcumin, Selenium, B Complex Vitamins, Iron, and Vitamin D. Evidence suggests that selenium (Se) supplementation could be useful as an adjunctive therapy to levothyroxine (LT4) in the treatment of Hashimoto's thyroiditis (HT) [41]. It has also been emphasized that compliance with nutritional guidelines may help thyroiditis of Hashimoto (TH) patients to reduce the need for medicines [42]. Antioxidant, anti-inflammatory, and immunomodulatory properties of food like mushrooms, which are natural sources of food and antioxidant are considered important in human health and helpful to HT disease patients. The consumption of dietary antioxidants protects against free radical damage for the prevention of various diseases and aging [43]. Six anti-inflammatory plant food supplements/Medicinals investigated by Chiara *et al.* [44] showed Boswellia serrata Roxb. was found to be the most promising, since it shows the best efficacy for treatment of pain/inflammatory conditions. But its efficacy in the management of HT remains to be further investigated.

7. Common Thyroid Gland Disorders Compared to Hashimoto's Disease

There are several common disorders that affect the thyroid gland, including hypothyroidism, goiter, hyperthyroidism, Graves' disease, thyroid nodules, and thyroid cancer. While Hashimoto's disease is the main cause of hypothyroidism, meaning that the resulting symptoms are the same, the difference between the two is that the immune system is the cause with Hashimoto's while a problem with the thyroid itself can be a cause of hypothyroidism [9]. Goiter can be a sign of Hashimoto's disease, or it could occur separately. There are diverse types of goiters, depending on whether the swelling is caused by too little or too much thyroid hormone, a lack of iodine (which is needed for thyroid hormone production), Thyroid nodules, or other causes and "[i]n the U.S., the main causes of

goiters are autoimmune disorders, including Graves' disease or Hashimoto's disease, and multinodular goiter" [10]. While Hashimoto's generally leads to hypothyroidism, in very few cases it can result in "the release of too much thyroid hormone into your blood, causing symptoms of hyperthyroidism" [45]. Hyperthyroidism mainly results in having too much thyroid hormone in the blood, and it can be caused by Graves' disease, nodules, too much iodine, or if a person with hypothyroidism or even Hashimoto's disease, takes an excessive amount of thyroid hormone supplements [10] [45]. Graves' Disease is a common autoimmune condition that causes hyperthyroidism and can increase a person's risk for developing a different autoimmune disorder, like Hashimoto's disease [45]. It is like Hashimoto's in that the body's immune system is what is causing the condition. With Graves' disease, the immune system attacks the thyroid gland and causes an increased production of thyroid hormone while affecting the negative feedback loop and preventing it from decreasing thyroid hormone production [45]. Thyroid nodules are located on the thyroid gland and can cause goiter or hyperthyroidism, but usually the nodules are not harmful [46]. Thyroid cancer is different from Hashimoto's disease since it is an abnormal growth of tissue in the thyroid gland instead of a problem with the immune system. There are different forms of thyroid cancer depending on its targeted area, but most are easily treated [40]. Each of these conditions is like Hashimoto's as regards their effects on the thyroid gland or thyroid hormone production, but they are different in their etiology [40].

8. Conclusion

Hashimoto's disease causes the body's immune system to affect the thyroid gland and thereby its hormone production. This can lead to several symptoms, and it is the leading cause of hypothyroidism. The low levels of T3 and T4 affect the body's ability to maintain homeostasis through metabolic activities and affect energy levels because of the low metabolism. Middle-aged females with a family history of Hashimoto's disease are most at risk for developing the autoimmune condition. Once the symptoms of the disease develop and the doctor is consulted, medical testing of the blood is required to confirm the diagnosis. After diagnosis, the treatment involves managing the symptoms and replacing the hormones that are low. The thyroid gland can also be affected by several other disorders, either separately or along with Hashimoto's disease, and each causes similar problems to occur with thyroid hormone production and secretion. In addition to the pharmacological agents that are useful in the management of the disease, several food and supplements have been reported to help TH patients.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Hashimoto's Disease—A Frame Diagram. Self Design.

[2] Hashimoto, H. (1912) Zur Kenntniss der Lyphomatosen Verandererung Schilddruse (*Struma lymphomatosa*). *Arch Klin Chirugie*, **972**, Article No. 219.

[3] Dunkin, M.A. (2020) Hashimoto's Thyroiditis: Symptoms, Causes, and Treatments. https://www.webmd.com/women/hashimotos-thyroiditis-symptoms-causes-treatments

[4] Bancos, I. (2018) Thyroid and Parathyroid Hormones. Endocrine Society. https://www.endocrine.org/patient-engagement/endocrine-library/hormones-and-endocrine-function/thyroid-and-parathyroid-hormones

[5] Diagram of the Thyroid Gland (n.d.) Enliven Wellness. https://www.enlivenwv.com/hashimotos-thyroid

[6] U.S. Department of Health and Human Services (2018) Hashimoto's Disease. National Institute of Diabetes and Digestive and Kidney Diseases.

[7] LDNscience-MedInsight Research Institute (2022) Hashimoto's Symptoms. https://10faq.com/health/hashimotos-disease-symptoms

[8] Kat. (2019) Hashimoto's Symptoms Checklist. Tons of Goodness. https://tonsofgoodness.com/my-experience-with-hashimotos-symptoms-diagnosis-and-treatment

[9] Gard, R.P. (2005) Human Endocrinology. Taylor & Francis Ltd., Arbingdon, Oxon, 50-55.

[10] Nazario, B. (2021) Goiter. WebMD. https://www.webmd.com/women/understanding-goiter-basics

[11] Hormone (2021) Thyroid Hormones. Hormone Health Network. https://www.hormone.org/your-health-and-hormones/glands-and-hormones-a-to-z/hormones/thyroid-hormones

[12] Davis, L.E., Leveno, K.J. and Cunningham, F.G. (1988) Hypothyroidism Complicating Pregnancy. *Obstetrics and Gynecology*, **72**, 108-112.

[13] Mizgala, L., Lao, T.T. and Hannah, M.E. (1991) Hypothyroidism Presenting as Hypothermia Following Pre-Eclampsia at 23 Weeks Gestation. *British Journal of Obstetrics and Gynaecology*, **98**, 221-224. https://doi.org/10.1111/j.1471-0528.1991.tb13374.x

[14] Leung, A.S., Millar, L.K., Koonings, P.F., Montoro, M. and Mestman, J. (1993) Pernatal Outcome in Hypothyroid Pregnancies. *Obstetrics and Gynecology*, **81**, 349-353.

[15] Abalovich, M., Gutierrez, S., Alcaraz, G., Maccallini, G., Garcia, A. and Levalle, O. (2002) Overt and Subclinical Hypothyroidism Complicating Pregnancy. *Thyroid*, **12**, 63-68. https://doi.org/10.1089/105072502753451986

[16] Glinoer, D., Rihi, M., Grun, J.F. and Kinthaert, J. (1994) Risk of Subclinical Hypothyroidism in Pregnant Women with Asymptomatic Thyroid Disorders. *The Journal of Clinical Endocrinology and Metabolism*, **79**, 197-204. https://doi.org/10.1210/jcem.79.1.8027226

[17] Casey, B.M., Dashe, J.S., Wells, C.E., McIntire, D.D., Byrd, W., Leveno, K.J. and Cunningham, F.G. (2005) Suclinical Hypothyroidism Is Associated with Premature Delivery. *Obstetrics and Gynecology*, **105**, 239-245. https://doi.org/10.1097/01.AOG.0000152345.99421.22

[18] Ruggeri, R.M., Trimarchi, F., Guiffrida, G., *et al.* (2017) Autoimmune Comorbidities in Hashimoto's Thyroiditis: Different Patterns of Association in Adulthood and Childhood and Childhood/Adolescence. *European Journal of Endocrinology*, **176**, 133-141. https://doi.org/10.1530/EJE-16-0737

[19] Control of Endocrine Activity (n.d.) Vivo Pathophysiology. http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/basics/control.html#:~:text=When%20blood%20concentrations%20of%20thyroid,example%20of%20%22negative%20feedback%22

[20] Arrangoiz, R., Cordera, F., Caba, D., *et al.* (2018) Comprehensive Review of Thyroid Embryology, Anatomy, Histology, and Physiology for Surgeons. *International Journal of Otolaryngology and Head & Neck Surgery*, **7**, 160-188. https://www.researchgate.net/figure/Hypothalamic-pituitary-thyroid-axis_fig10_326375395

[21] Shira, E. (2022) Do I Have Hashimoto' Disease (Thyroiditis). https://endocrineWeb.com/conditions/hashimoto's-thyroiditis

[22] Ajjan, R.A. and Weetman, A.P. (2015) The Pathogenesis of Hashimoto's Thyroiditis: Further Develops in Our Understanding. *Hormone and Metabolic Research*, **47** 702-710. https://doi.org/10.1055/s-0035-1548832

[23] Weetman, A.P. (2005) Non-Thyroid Autoantibodies in Autoimmune Thyroid Disease. *Best Practice & Research Clinical Endocrinology & Metabolism*, **19**, 17-32. https://doi.org/10.1016/j.beem.2004.11.004

[24] Penta, L., Cofini, M., Lanciotti, L., Leonardi, A., Principi, N. and Esposito, S. (2018) Hashimoto Disease and Thyroid Cancer in Children: Are They Associated? *Frontiers in Endocrinology* (*Lausanne*), **9**, 565. https://doi.org/10.3389/fendo.2018.00565

[25] Mayo Foundation for Medical Education and Research (2020) Hypothyroidism (Underactive Thyroid). Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/hypothyroidism/symptoms-causes/syc-20350284

[26] Ragusa, F., Fallahi, P., Elia, G., *et al.* (2019) Hashimotos' Thyroiditis: Epidemiology, Pathogenesis, Clinic, and Therapy. *Best Practice & Research Clinical Endocrinology & Metabolism*, **33**, Article ID: 101367. https://doi.org/10.1016/j.beem.2019.101367

[27] Mayo Foundation for Medical Education and Research (2020) Hashimoto's Disease. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/hashimotos-disease/diagnosis-treatment/drc-20351860

[28] Maeda, S.S., Fortes, E.M., Oliveira, U.M., Borba, V.C. and Lazaretti-Castro, M. (2006) Hypoparathyroidism and Pseudohypoparathyroidism. *Arquivos Brasileiros de Endocrinologia & Metabologia*, **50**, 664-673. https://doi.org/10.1590/S0004-27302006000400012

[29] Bollerslev, J., Rejnmark, L., Marcocci, C., Shoback, D.M., Sitges-Serra, A., van Biesen, W., *et al.* (2015) European Society of Endocrinology Clinical Guideline: Treatment of Chronic Hypoparathyroidism in Adults. *European Journal of Endocrinology*, **173**, G1-G20. https://doi.org/10.1530/EJE-15-0628

[30] Shoback, D. (2008) Clinical Practice. Hypoparathyroidism. *New England Journal of Medicine*, **359**, 391-403. https://doi.org/10.1056/NEJMcp0803050

[31] Clarke, B.L., Brown, E.M., Collins, M.T., Juppner, H., Lakatos, P., Levine, M.A., *et al.* (2016) Epidemiology and Diagnosis of Hypoparathyroidism. *The Journal of Clinical Endocrinology and Metabolism*, **101**, 2284-2299. https://doi.org/10.1210/jc.2015-3908

[32] Sergio, S.M., Marise, L.-C., *et al.* (2018) Diagnosis and Treatment of Hypothyroidism: A Position Statement from the Brazilian Society of Endocrinology and Metabolism. *Archives of Endocrinology and Metabolism*, **62**, 106-124.

[33] Morris, E.D., Stuart, L. and Richard, S. (1995) Relation of Thyroid Neoplasms to Hashimoto Disease of the Thyroid Gland. *American Medical Association Archives of Surgery*, **70**, 291-297. https://doi.org/10.1001/archsurg.1955.01270080137023

[34] Kilfoy, B., Zheng, T., Holford, T., *et al.* (2009) International Patterns and Trends in Thyroid Cancer Incidence, 1973-2002. *Cancer Causes and Control*, **20**, 525-531. https://doi.org/10.1007/s10552-008-9260-4

[35] Norman, J. and Kopf, J. (2021) What Is Hypothyroidism? Endocrine Web. https://www.endocrineweb.com/conditions/hypothyroidism

[36] Plexus Professional Network Private Limited (2021) A Third Discontinuing Levothyroxine Have Normal Thyroid Levels. Plexus MD. https://www.plexusmd.com/md/post/a-third-discontinuing-levothyroxine-have/64073

[37] X-Gen Pharmaceuticals (n.d.) Showing Pharmacological Agents—Liothyronine Sodium. https://www.mountainside-medical.com/products/liothyronine-sodium-for-injection-t3-thyroid-hormone-agent-1ml

[38] Eghtedari, B. and Correa, R. (2022) Levothyroxine. National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK539808/

[39] Davis, C.P. (2021) Hyperthyroidism: Symptoms, Treatment, Medication. MedicineNet. https://www.medicinenet.com/hyperthyroidism_pictures_slideshow/article.htm

[40] Roberto, N., Gianni, F., Tiziana, M., Antonio, P., Davide, D. and Haslinda, H. (2006) Levothyroxine Treatment in Euthyroid Pregnant Women with Autoimmune Thyroid Disease: Effects on Obstetrical Complications. *The Journal of Clinical Endocrinology & Metabolism*, **91**, 2587-2591. https://doi.org/10.1210/jc.2005-1603

[41] Toulis, K.A., Anthanasios, D.A., Thrasivoulos, G.T., Dimitrios, G.G. and Kouvelas, D. (2010) Selenium Supplementation in the Treatment of Hashimoto's Thyroiditis: A Systematic Review and a Meta-Analysis. *Thyroid*, **20**, 1163-1173.

[42] Yana, D., Tsevetelina, V., Georgi, N., Zorka, M., Alexander, S., Hristo, G. and Rossitza, K. (2022) Nutritional Management of Thyroiditis of Hashimoto. *International Journal of Molecular Sciences*, **23**, Article No. 5144. https://doi.org/10.3390/ijms23095144

[43] Carmen, S. (2017) Reactive Oxygen Species and Antioxidant Properties from Mushrooms. *Synthetic and Systems Biotechnology*, **2**, 13-22. https://doi.org/10.1016/j.synbio.2016.12.001

[44] Di Lorenzo, C., Dell'agli, M., Badea, M., Lorena, D., *et al.* (2013) Plant Food Supplements with Anti-Inflammatory Properties: A Systematic Review (II). *Critical Reviews in Food Science and Nutrition*, **53**, 507-516.

[45] U.S. Department of Health and Human Services (2021) Graves' Disease. National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/endocrine-diseases/graves-disease

[46] Mayo Foundation for Medical Education and Research (2022) Thyroid Nodules. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/thyroid-nodules/symptoms-causes/syc-20355262#:~:text=Thyroid%20nodules%20are%20solid%20or,of%20thyroid%20nodules%20are%20cancerous