The Science Journal of the Lander College of Arts and Sciences

The Science Journal of the Lander College of Arts and Sciences

Volume 14
Number 2 *Spring 2021*

64-69

2021

Do People with Hashimoto's Disease need a Thyroidectomy?

Miriam Minkowitz

Do People with Hashimoto's Disease need a Thyroidectomy?

Miriam Minkowitz

Miriam Minkowitz will graduate with a Bachelor of Science degree in Honors Biology in June 2021

Abstract

Hashimoto's Thyroiditis (HT) is one of the most common autoimmune diseases (Hiromatsu et al. 2013 p.13). It primarily affects the thyroid gland. The thyroid gland influences growth and regulates the body's metabolism by manipulating hormonal levels. Hashimoto's thyroiditis affects thyroid function through mechanisms that cause the hormone levels to become dysregulated. The standard therapy for Hashimoto's thyroiditis is hormone replacement. This approach helps most patients by regulating their thyroid hormones, though there are some individuals who fail treatment. Untreatable patients are plagued with weight gain, sleep disturbances, and other symptoms. Certain factors in thyroid disease may cause various secondary complications including psychiatric manifestations. Research into these patients has shown that the removal of the thyroid gland seems to improve their clinical condition. Therefore, in the situation when significant symptoms remain after what appears to be adequate medicinal treatment, the possibility of surgery should be entertained. This review discusses the pathological underpinnings of Hashimoto's disease and reviews some of the published literature from the past ten years in relation to the treatment of HT.

Introduction

The thyroid gland is a butterfly-shaped endocrine gland found in the lower front portion of the neck. The thyroid primarily controls metabolic function. This includes hormone production, growth, and bodily maturation. Thermoregulation, as well as brain maturation and other cognitive functions, are also controlled by the thyroid (Drake 2018). Thyroid dysfunction can be due to hyperthyroidism, the overproduction of thyroid hormone, or hypothyroidism, which is the underproduction of hormones. The most common symptoms of hyperthyroidism are weight loss and palpitations, while the most common symptoms of hypothyroidism are weight gain and lethargy (Guyton, Hall 2006 Pp. 938-940).

According to the American Thyroid Association (ATA), there are approximately twenty-million people in the United States who suffer from thyroid disease. Of this twenty-million, about fourteen million of them suffer from an autoimmune condition known as Hashimoto's thyroiditis (American Thyroid Association, General Information). An autoimmune disease develops when the body's immune system begins attacking its own organs or particular proteins. Autoimmune diseases are caused by autoantibodies, which respond to normal organs as foreign invaders. Hashimoto's Thyroiditis occurs when the body attacks either the thyroid cells or their product thyroxine.

Hashimoto's Thyroiditis can develop in patients with either a genetic or environmental susceptibility (Pyzik et al. 2015). Hiromatsu et al. studied some of the current concepts of genetic susceptibility to Hashimoto's Thyroiditis. They noted that, specifically, the concordance rate for HT in identical twins (monozygotic) is 55%, while in non-identical twins (dizygotic) it is 0%. Moreover, they also observed that there is a higher rate of concordance of thyroid autoantibodies not associated with Hashimoto's Thyroiditis in monozygotic twins than in dizygotic twins. In these siblings, 80% of monozygotic twins had autoantibodies versus 40% in nonidentical twins (Hiromatsu et al. 2013). This study concluded that genetics is a significant factor in HT.

Several genetic loci have also been identified as associated with Hashimoto's thyroiditis, most notably multiple human leukocyte antigen-DR (HLA-DR) isotopes. HLA-DR is a lymphocyte surface receptor. When genetically altered it affects what is presented to the T-cells which elicits an immunologic response. This response can influence the selectivity and binding of peptides, which appears to predispose individuals to the development of HT (Hiromatsu et al. 2013). Other immune modulators released from the lymphocytes, such as interferon-gamma can also instigate the development of HT.

Environmental triggers that affect individuals susceptible to Hashimoto's thyroiditis include infections, dietary factors, and pregnancy. Although iodine deficiency can cause thyroid diseases, excess iodine can induce autoimmunity by increasing the body's sensitivity to abnormal thyroglobulin. Thyroglobulin is the protein produced by the thyroid and is the precursor to the thyroid hormones triiodothyronine (T3) and thyroxine (T4). In the presence of excess iodine, thyroglobulin can be abnormally iodinated. This can lead to the production of autoantibodies as well as to the toxicity of the thyroid cells and hypothyroidism (Hiromatsu et al. 2013).

With all this in mind, the two main autoantibodies linked to Hashimoto's Thyroiditis are anti-thyroglobulin and antithyroid peroxidase. An anti-thyroglobulin antibody binds to thyroglobulin which limits availability and subsequent release of T3 and T4 thyroid hormones. The thyroglobulin directly affects the functional aspect of the thyroid and its reduction, or absence contributes to a patient's hypothyroid symptoms. Antithyroid peroxidase, on the other hand, targets thyroid follicular cells or thyrocytes. The way it does this is by tagging the thyroid cells for destruction which can in turn lead to hypothyroidism. HT is an insidious disease that can take years before becoming clinically significant (Guyon, Hall 2006, Pp. 940-943).

Many patients eventually require treatment with thyroid hormone replacement. This therapy involves being prescribed a bio-identical thyroid hormone medication,

such as Levothyroxine also known as Synthroid or Armor Thyroid. For most patients, the treatment works well, and the symptoms are resolved. There are circumstances though where hormone replacement fails and in cases like these clinical research has shown that the surgical excision of the thyroid or thyroidectomy should be considered. This potentially works because it reduces the antibody load and the antibody's potential effects on other targets (Goldvog et al. 2019, p. 462). The main objective of this paper is to review the possible solutions to treatment-resistant Hashimoto's thyroiditis disease.

Methods

Data was collected through Touro College's online library using several scientific scholarly databases such as ProQuest and PubMed databases. The key-phrases used were Hashimoto's Disease, Hashimoto's thyroiditis, thyroidectomy, and autoimmune thyroiditis. Only peer-reviewed journals and English language articles were analyzed.

Discussion

Autoimmune thyroid disease was first described in 1912 by the Japanese surgeon Hakaru Hashimoto (Pyzik et al. 2015). He identified a cohort of patients with lymphoid infiltration of the thyroid with associated destruction of the thyroid glands which he called "struma lymphomatosa" (Hiromatsu et al. 2013). The concept of autoimmune diseases was not recognized until the 1950s and even currently many of these diseases are not fully understood. Hypothyroidism is diagnosed by a thyroid function blood test that shows elevated thyroid stimulating hormone (TSH) which reflects a reduction in the thyroid's function (Drake 2018). Unlike many other diseases, patients who suffer from hypothyroidism do not exhibit symptoms over a set timeline. Some patients develop their symptoms over days to months, while for others, symptoms evolve over years to decades (Lee 2020). In other words, hypothyroidism can exist in many states which can range from a subclinical harmless state to a significant clinical presentation (Chaker et al. 2017). Table 1 shows a flow chart on the process of diagnosing the disease.

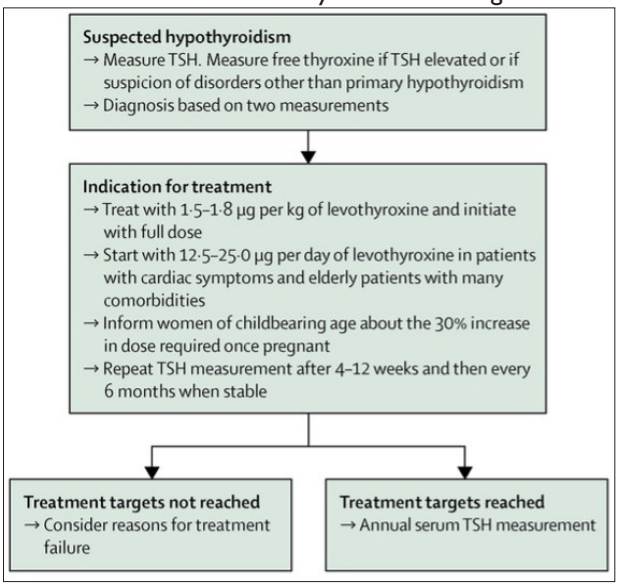

Table1: Diagnostic scheme (Chaker et al. 2017)

There is controversy as to when medical professionals should start treating patients with clinical hypothyroidism. According to the American Association of Clinical Endocrinology (AACE) guidelines, there are a few opinions as to when treatment commences. Treatment generally relies on the Thyroid Stimulating Hormone (TSH) level. TSH responds to feedback inhibition of the pituitary gland, the organ which produces TSH. As the levels of thyroid hormone increase, the TSH decreases, and as the levels of thyroid hormone decrease the TSH increases. This is an example of a negative feedback loop (Guyon, Hall 2006, p. 939). The American Thyroid Association's guidelines suggest that when the TSH levels approach 10 mIU/L patients are clinically hypothyroid and need treatment. Others claim that there are therapeutic reasons to start treating at lower levels. Regardless, treatment is always dependent on the clinical symptoms being addressed (Garber et al. 2012, p. 1112).

The most common symptoms of hypothyroidism in adults are weight gain, fatigue, hot/cold intolerance, and memory loss (brain fog). Table 2 lists the signs and symptoms related to hypothyroidism. The symptoms for the diagnosis of hypothyroidism are reflective of the hormonal insufficiency in different organs (Carle et al. 2014, p. 593). Symptoms vary by age and health status. An increase in the severity of symptoms may predict a harsher course of hypothyroidism. Clinical symptoms were originally used to diagnose hypothyroidism. A variety of outdated scoring systems such as the Billewicz score system and the Zulewski score system were utilized. With the advent of a sensitive blood test for TSH, these systems have been phased out and the fluctuation in TSH levels is what is used to guide the treatment of the disease.

Thyroid function has also been proven to play a crucial role in the cognitive development of youth and many other facets regulating nervous system activity. Neuropsychiatric symptoms refer to a gamut of emotional and cognitive complications that are directly related to alterations in the brain (Dickerman, Barnhill 2012). Due to the close association between thyroid and the nervous system function, disturbances in the body's

TABLE. Signs and Symptoms of Hypothyroidism

Signs	Symptoms
Eyebrow and hair thinning (C)	Fatigue
Skin coarsening (C)	Weight gain
Tendon relaxation phase slowing (C)	Cold intolerance
Facial/periorbital edema (O)	Mental slowing
Macroglossia (O)	Muscle weakness
Bradycardia (O)	Reduced exercise capacity
Pericardial effusion (R)	Constipation
Pleural effusion (R)	Xeroderma
Rhabdomyolysis (R)	Depression
	Menstrual irregularities

C = common; O = occasional; R = rare.

metabolic state can be related to a range of neurological signs and symptoms. These signs include headaches, mood, and cognitive disorders, ophthalmoplegia (eye movement disorder), tremors, and muscle weakness. Hypothyroidism can cause psychiatric symptoms such as depression, anxiety, memory deficits, and even psychosis. According to medical guidelines, testing for thyroid disease is a case-by-case decision, but patients who present with psychiatric issues should all be screened for thyroid dysfunction (Dickerman, Barnhill 2012, p.130).

In the neuropsychiatric realm, a sudden worsening in a patient's hypothyroidism may result in myxoedema coma, a life-threatening condition that is also associated with a rapid decline in mental health. The degree to which subclinical hypothyroidism and mild hypothyroidism impacts moods and cognitive functions, as well as whether these symptoms respond to treatment, remains controversial (Stasiolek 2015). A case study reported a 61-year-old woman who first presented to the emergency room complaining of severe chronic daily headaches. According to the patient, the headaches started 9 months prior and were described as, "bi-lateral with pressing-type quality, without associated symptoms such as nausea, photophobia, and did not worsen with exercise,". The patient also presented with depressive symptoms which were evaluated by a psychiatrist. The woman was subsequently diagnosed as having depressive syndrome. She was prescribed antidepressants but the medication failed to correct the problem. The patient later had a full medical evaluation which included blood work. The blood work revealed an increased anti-TPO antibody titer. This patient was diagnosed with encephalopathy related to autoimmune thyroid disease, which is also known as Hashimoto's encephalopathy (Correia et al. 2019).

Another physical ailment associated with hypothyroidism is reduced cardiac output. This is a result of the relaxation of vascular smooth muscle tissue. This relaxation occurs because the thyroid hormones which control the pacemaker-related genes reduce the heart rate and cardiac output which subsequently increases arterial stiffness leading to hypertension. (Udovcic et al. 2017, p. 55). Because of this process, a person's heart rate will elevate in the presence of excess thyroid hormone (hyperthyroidism) or reduce if the person has less thyroid hormone present (hypothyroidism). The change from normal levels to abnormal levels produces a domino effect of increased arterial stiffness, which then causes increased systemic vascular resistance. A variety of medicinal conditions can arise due to these changes which include atrial fibrillation and heart failure (Udovcic et al. 2017).

Thyroid dysfunction can also be associated with changes in body temperature and body weight. The thyroid-stimulating hormone regulates the basal metabolism, thermogenesis, and lipid glucose metabolism (Sanyal, Raychaudhuri 2016). "According to the National Health and Nutrition Examination Survey, obesity affected 32.2% of adults in 2003–2004." (Biondi 2010, p. 3614). A study performed in India at the Medwin Hospital's department of Endocrinology and Obesity Clinic found that thyroid dysfunction was realized more in individuals that were obese. All the patients included in the study underwent a physical examination which included, "Height, weight, waist circumference, presence of goiter, acanthosis nigricans or peripheral stigmata of dyslipidemia and blood pressure measurement," (Verma et al. 2008). Their study consisted of a total of 1075 patients. The study was divided into two subgroups. One group was made up of 625 patients who were enrolled in the hypothyroidism clinic, and the other group was 450 patients who were enrolled in the obesity clinic. Of the patients from the hypothyroidism clinic, 44% of them found that their body mass index (BMI) was greater than 25 kg/m2 with the typical BMI for a healthy person being anywhere between 18.5 and 24.9 kg/m2. Of the patients from the obesity clinic, only 33% had hypothyroidism (Verma et al. 2008). They concluded that most people who suffer from hypothyroidism have the likelihood of being obese.

Thyroid glands are also prone to develop nodules known as goiters. A goiter refers to an abnormal enlargement within the thyroid gland. It is important to stress that the majority of people that have goiters do not have any thyroid gland dysfunction. People with Hashimoto's

thyroiditis, however, seem to have more nodules than the average person. This leads to patients with Hashimoto thyroiditis having a slightly higher risk of developing thyroid cancer (Fish 2019 p.334). Some researchers say that the higher rate for papillary thyroid carcinoma is due to the presence of an autoimmune-response, or possibly anti-tumor immune response to the immune mediators (Graceffa et al. 2019, p.5).

As mentioned previously in this paper, the primary treatment for Hashimoto's disease consists of hormone replacement. Hormone replacement aims to balance the patient's biochemical system. While taking out the thyroid might prevent an antibody response, if a patient does not have a significant quality of life issue, doctors would not suggest having a total thyroidectomy (Promberger et al. 2014, p. 979). There are cases in which a patient is still affected by the symptoms of hypothyroidism, even after taking the correct dosage of medication and correcting the abnormal TSH level. In that instance, doctors might suggest that the patient undergo a total thyroidectomy (Pollock et al. 2001, p.894).

There are some standard indications as to when it is appropriate to have a thyroidectomy beyond having thyroid cancer. When a patient starts to exhibit compressive symptoms such as discomfort while swallowing, the feeling of strangulation, or tightness in the neck, it is appropriate to surgically remove the thyroid gland (Pradeep et al. 2011). Greater than 63% of patients with HT identified with the symptom of compression (McManus et al. 2011, p. 336). Another symptom that hormone replacement cannot cure is painful Hashimoto thyroiditis. Painful HT is also known as acute exacerbation of HT. This condition is not very common and in most instances is treated adequately with painkillers. Having a total thyroidectomy is thought to be the best treatment for this condition especially when painkillers do not provide relief (Peng et al. 2020, p.12).

In certain instances, patients with Hashimoto's disease may not necessarily experience a resolution of their complaints with medication. A study of 426 women who were all planning on having their thyroids removed for various reasons including HT. Before surgery, they all answered the SF-36 questionnaire, which is a set of generic, and easily administered quality-of-life measurements. The results established that patients who had high anti-TPO levels had lower quality of life measures even though they were taking the correct dosage of medication based on their TSH levels (Ott et al. 2011, p.165).

In the Annals of Internal Medicine, Guldvog et al., who performed the first randomized controlled trial, demonstrated that the removal of the thyroid gland in patients with histologically verified Hashimoto's disease can improve their quality of life by normalizing their anti-TPO antibody titer levels. This study was performed on patients between the ages of 18 to 79 years. They all had anti-TPO titers above 1000 IU/ml (normally less than 35 IU/ml). In total there were 150 test subjects all of whom had persistent Hashimoto-related symptoms. Before the data was collected and the surgery was performed, all the patients were monitored for thyroid function until they achieved euthyroid status or normal thyroid function. Participants were either assigned to undergo total thyroidectomy with continued hormone replacement or to only receive hormone replacement therapy. After 18 months, the anti-TPO levels of the surgical group had fallen from a mean of 2232 IU/ml to 152 IU/ml, and the general health score of the surgical group improved from 38 to 64 points. The chronic fatigue frequency in the surgical group decreased from 82% to 35% of the individuals. The overall score was improved compared to the original SF-36 questionnaire. The control group showed no significant changes. The researchers hypothesized that the improvement in symptoms could be related to the normalization of serum anti-TPO antibody titers. (Goldvog et al. 2019).

Dr. Trevor Angell interpreted and reviewed the study done by Guldvog et al. and concluded that the results were compelling. Guldvog et al. indicates that patients with Hashimoto's thyroiditis might have persistent symptoms due to more than just the thyroid dysfunction. They found that a thyroidectomy may modulate the immune response by removing the antigen and thereby reducing the inflammation and the inflammatory mediators. With the removal, the symptoms caused by HT would subsequently be alleviated (Angell 2019, p.180).

Nevertheless, the initial plan of treatment for patients who have the symptoms of hypothyroidism should be supplemental hormone replacement. In the case when patients do not respond positively to hormone replacement, a total thyroidectomy has proven to be effective as well. For a patient that chooses to have surgery, a risk analysis of surgical complications must be evaluated. One study predicted that if more people start removing their thyroids then complications will increase 12-fold. This rate, according to the literature, would change from 3.05% to 36.6% (Memeh et al. 2020).

Conclusion

In conclusion, not every person who has Hashimoto's thyroiditis should have thyroid surgery. According to the research reviewed, having a thyroidectomy might only be recommended to patients who have Hashimoto's Thyroiditis and who are experiencing neuropsychiatric symptoms after their TSH levels are stabilized. There

needs to be more research evaluating and specifying the benefits of having a thyroidectomy. Larger test groups need to be observed, and the follow-up period should be extended. Though they are not frequent, complications of total thyroidectomy are real, and the risk-benefit ratio must be assessed on a case by case basis.

References

American thyroid association.general information/press room . https://www.thyroid.org/media-main/press-room/

Angell, T. E. (2019). Thyroidectomy Improves Quality of Life and Fatigue in Patients with Hashimoto's Disease and Persistent Symptoms Compared to Adequate Thyroid Hormone Replacement. Clinical Thyroidology, 31(5), 178-181. https://10.1089/ct.2019;31.178-181

Biondi, B. (2010). Thyroid and Obesity: An Intriguing Relationship. The Journal of Clinical Endocrinology and Metabolism, 95(8), 3614-3617. https://10.1210/jc.2010-1245

Carlé, A., Pedersen, I. B., Knudsen, N., Perrild, H., Ovesen, L., & Laurberg, P. (2014). Hypothyroid symptoms and the likelihood of overt thyroid failure: a population-based case–control study. European Journal of Endocrinology, 171(5), 593-602. https://10.1530/EJE-14-0481

Chaker, L., Bianco, A. C., Jonklaas, J., & Peeters, R. P. (2017). Hypothyroidism. The Lancet (British Edition), 390(10101), 1550-1562. https://10.1016/S0140-6736(17)30703-1

Correia,I., Marques, I. B., Ferreira, R., & Sousa, L. (2016). Encephalopathy Associated with Autoimmune Thyroid Disease: A Potentially Reversible Condition. Case Reports in Medicine, 2016, 1-6. https://10.1155/2016/9183979

Dickerman, A. L., & Barnhill, J. W. (2012). Abnormal Thyroid Function Tests in Psychiatric Patients: A Red Herring? American Journal of Psychiatry, 169(2), 127-133. https://10.1176/appi.ajp.2011.11040631

Drake, M. T. (2018). Hypothyroidism in Clinical Practice. Mayo Clinic Proceedings, 93(9), 1169-1172. https://10.1016/j.mayocp.2018.07.015

Fish, S. A. (2019). Hashimoto's Thyroiditis Is a Risk Factor for Thyroid Cancer. Clinical Thyroidology, 31(8), 333-335. https://10.1089/ct.2019;31.333-335

Garber, J., Cobin, R., Gharib, H., Hennessey, J., Klein, I., Mechanick, J., Pessah-Pollack, R., Singer, P., & Woeber, K. (2012). Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocrine Practice, 18(6), 988-1028. https://10.4158/ep12280.gl

Graceffa, G., Patrone, R., Vieni, S., Campanella, S., Calamia, S., Laise, I., Conzo, G., Latteri, M., & Cipolla, C. (2019). Association between Hashimoto's thyroiditis and papillary thyroid carcinoma: a retrospective analysis of 305 patients. BMC Endocrine Disorders, 19(Suppl 1), 26. https://10.1186/s12902-019-0351-x

Guldvog, I., Reitsma, L. C., Johnsen, L., Lauzike, A., Gibbs, C., Carlsen, E., Lende, T. H., Narvestad, J. K., Omdal, R., Kvaløy, J. T., Hoff, G., Bernklev, T., & Søiland, H. (2019). Thyroidectomy Versus Medical Management for Euthyroid Patients With Hashimoto Disease and Persisting Symptoms: A Randomized Trial. Annals of Internal Medicine, 170(7), 453-464. https://10.7326/M18-0284

Guyton, A., & Hall, J. (2006). Textbook of Medical Physiology (Eleventh ed.). Elsevier Saunders.

Hiromatsu, Y., Satoh, H., & Amino, N. (2013). Hashimoto's Thyroiditis: History and Future Outlook. Hormones (Athens, Greece), 12(1), 12-18. https://10.1007/bf03401282

Lee Stephanie, L. (2020). Hashimoto Thyroiditis. https://emedicine.medscape.com/article/120937-overview?src=ppc_google_rlsa-traf_mscp_emed-mid-cohort-hdhm-cohort_md_us

McManus, C. M., Luo, J., Sippel, R., & Chen, H. (2011). Should Patients With Symptomatic Hashimoto's Thyroiditis Pursue Surgery? The Journal of Surgical Research, 165(2), 336. https://10.1016/j.jss.2010.11.176

Memeh, K., Ruhle, B., Vaghaiwalla, T., Kaplan, E., Keutgen, X., & Angelos, P. (2020). Thyroidectomy for euthyroid patients with Hashimoto thyroiditis and persisting symptoms: A cost-effectiveness analysis. Surgery, 169(1), 7-13. https://10.1016/j.surg.2020.03.028

Ott, J., Promberger, R., Kober, F., Neuhold, N., Tea, M., Huber, J. C., & Hermann, M. (2011). Hashimoto's Thyroiditis Affects Symptom Load and Quality of Life Unrelated to Hypothyroidism: A Prospective Case–Control Study in Women Undergoing Thyroidectomy for Benign Goiter. Thyroid (New York, N.Y.), 21(2), 161-167. https://10.1089/thy.2010.0191

Peng, C. C., Munir, K. M., Song, L., Papadimitriou, J. C., & Pennant, M. A. (2020). RECURRENT PAINFUL HASHIMOTO THYROIDITIS SUCCESSFULLY TREATED BY THYROIDECTOMY. AACE Clinical Case Reports, 6(1), e9-e13. https://10.4158/ACCR-2019-0184

Pollock, M. A., Sturrock, A., Marshall, K., Davidson, K. M., Kelly, C. J. G., McMahon, A. D., & McLaren, E. H. (2001).

Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomised double blind placebo controlled crossover trial. Bmj, 323(7318), 891-895. https://10.1136/bmj.323.7318.891

Pradeep, P. V., Ragavan, M., Ramakrishna, B. A., Jayasree, B., & Skandha, S. H. (2011). Surgery in Hashimoto's thyroiditis: Indications, complications, and associated cancers. Journal of Postgraduate Medicine, 57(2), 120-122. https://10.4103/0022-3859.81867

Promberger, R., Hermann, M., Pallikunnel, S. J., Seemann, R., Meusel, M., & Ott, J. (2014). Quality of life after thyroid surgery in women with benign euthyroid goiter: influencing factors including Hashimoto's thyroiditis. The American Journal of Surgery, 207(6), 974-979. https://10.1016/j.amjsurg.2013.05.005

Pyzik, A., Grywalska, E., Matyjaszek-Matuszek, B., & Roliński, J. (2015). Immune Disorders in Hashimoto's Thyroiditis: What Do We Know So Far? Journal of Immunology Research, 2015, 1-8. https://10.1155/2015/979167

Sanyal, D., & Raychaudhuri, M. (2016). Hypothyroidism and obesity: An intriguing link. Indian Journal of Endocrinology and Metabolism, 20(4), 554-557. https://10.4103/2230-8210.183454

Stasiolek, M. (2015). Neurological symptoms and signs in thyroid disease. Thyroid Research, 8(Suppl 1), A25. https://10.1186/1756-6614-8-s1-a25

Udovcic, M., Pena, R. H., Patham, B., Tabatabai, L., & Kansara, A. (2017). Hypothyroidism and the Heart. Methodist DeBakey Cardiovascular Journal, 13(2), 55-59. https://10.14797/mdcj-13-2-55

Verma, A., Jayaraman, M., Kumar, Hari K. V. S, & Modi, K. D. (2008). Hypothyroidism and obesity : Cause or Effect? Saudi Medical Journal, 29(8), 1135-1138. https://www.ncbi.nlm.nih.gov/pubmed/18690306