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Hashimoto's Thyroiditis: An Integrative Nutrition Perspective

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Introduction

Chronic autoimmune thyroiditis, or Hashimoto's thyroiditis (HT) is the most common cause of hypothyroidism in areas of the world that are not deficient in iodine, making up about 95% of cases [1]. It is found in up to 10% of the population with females being much more impacted than males with a 7:1 female:male ratio [2]. Due to this, most healthcare practitioners will encounter this condition warranting a detailed understanding of the condition. For those practicing integrative medicine, many factors are considered when it comes to assessing a client with a particular condition and identifying a root cause approach and intervention. NIBLETS is a model for assessment that looks at seven components: Nutrient deficiencies/insufficiencies, Inflammation/immunity, Biochemical individuality, Lifestyle factors, Toxic load, and Stress/sleep [3]. This review will first describe HT and then review each NIBLETS section in relation to HT.

Description of Hashimoto's Thyroiditis

HT is characterized by destruction of thyrocytes by autoantibodies and lymphocyte infiltration and can have overt, clinical presentation or can be subclinical. Phenotypes include those with either goiter or atrophy present. Symptoms of clinical or subclinical hypothyroidism include fatigue, cold intolerance, weight gain, dyspnea upon exertion, dry skin, and edema [1].

Thyroid stimulating hormone (TSH) is typically the initial test performed when hypothyroidism is suspected, followed by a free thyroxine (T4) test and possibly triiodothyronine (T3). Classic presentation of overt hypothyroidism would be a TSH > 4 mU/L and free T4 < 0.9 ng/dL with T3 normal or slightly low. Laboratory features of Hashimoto's thyroiditis include presence of antibodies to thyroid peroxidase (TPO) and thyroglobulin (Tg). TPO antibodies may be measured along with TSH It should be stated that thyroiditis can be present with normal thyroid function tests, known as subclinical disease, so investigation of TPO autoantibody levels is warranted as subclinical disease can eventually result in clinical onset of overt hypothyroidism which is permanent most cases. However, measurement of TPO autoantibodies in those with normal thyroid function labs but classic symptoms of hypothyroidism is not routinely done in conventional healthcare [2].

Nutritional Deficiencies and Insufficiencies

Iodine, along with iron, selenium, vitamin B12, and vitamin D, are nutrients of concern in HT [4]. Iodine plays a role in the synthesis of thyroid hormones. It is a component of T4 and T3. A nodular goiter can result from insufficient iodine intake which can lead to thyroid antibodies being released from the abnormal thyroid gland. Conversely, excess iodine intake or increased intake after diet fortification in a previously iodine-deficient population can also result in an increased incidence of auto-immune thyroiditis. One mechanism that is thought to lead to this is that highly iodinated Tg leads to an autoimmune reaction to the thyroid gland. Due to this, iodine fortification in a country should be done with caution. Intake should be modified to achieve a median urinary iodine concentration of 100-200 micrograms/liter.

TPO, which is required for thyroid hormone synthesis, is dependent upon binding a heme group to become active [4]. Heme being an iron-containing molecule, means that adequate iron is central to the synthesis of thyroid hormones. Thus, iron deficiency leads to lower thyroid hormone production due to the lowered activity of TPO and may cause persistent symptoms in those being treated for hypothyroidism. Those with hypothyroidism should be screened for iron deficiency and treated accordingly.

Selenium deficiency is also associated with hypothyroidism [4]. The thyroid contains the largest amount of selenium in the body and selenoproteins, which are important to thyroid function, are expressed in thyrocytes. Glutathione peroxidases, a category of selenoproteins, seem to be particularly important in forming thyroid hormones. In a systematic review and meta-analysis on selenium supplementation in autoimmune thyroiditis, selenium was shown to significantly reduce TPO-antibodies at 6 months and both TPO antibodies and Tg-antibodies at 12 months [5]. Selenium supplementation has also been shown to reduce hypothyroidism incidence, and postpartum thyroiditis. A recent randomized controlled trial on HT patients in China [6] evaluated the role of Selenium (Se) supplementation (200 mcg selsnius yeast tablets) in patients with pre-existing HT. They found that those in the treatment group had decreased levels of TPOAb, TGAb, and TSH when Se levels were low. They also, when compared with the control group, had increases in Se. These results indicate that Se supplementation may be beneficial for those with HT who have low Se status.

Vitamin B-12 and vitamin D deficiency have been shown to be increased in patients with HT [7]. A 2020 study [7] investigated Vitamin B12 and vitamin D levels and their relationship to anti-TPO antibodies in those with HT. Vitamin B12 and vitamin D deficiency were found to

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be 46% and 56.1% respectively. The study found a negative correlation between both vitamin B12 deficiency and vitamin D deficiency and anti-TPO antibodies indicating deficiency may have a role in HT. This suggests a need to assess B12 and D status in patients with or at risk for HT.

Inflammation and Immune (Dys)regulation

The exact pathogenesis of HT is not fully understood. However, as it is an autoimmune disease, the immune system is known to play a role. It is also known that immune system dysfunction and production of autoantibodies to thyroid antigens plays a role in its pathogenesis [8]. Regulatory T cells (Tregs) play an important role in preventing autoimmune thyroid diseases and certain single nucleotide polymorphisms (SNPs) in the Foxp3 gene, the master regulator of Tregs, can cause low levels or impair their function.

It is known that the composition of the human microbiome plays a role in the immune response [9]. There is a reciprocal relationship between the human microbiota and the immune system; The development of the immune system is shaped by the microbiota and the microbiota are maintained by the intestinal barrier. Gut dysbiosis has been associated with the pathogenesis of autoimmune conditions, including thyroid autoimmunity.

There has been evidence suggesting that Hashimoto's thyroiditis (HT) is associated with gut dysbiosis, bacterial overgrowth, and leaky gut [10]. Changes at the intestinal level have been noted in patients with HT including colonic intraepithelial lymphocytes, increased thickness of microvilli in the distal duodenum, increased space between microvilli, and intestinal permeability. Also, lipopolysaccharide, a marker of impaired intestinal barrier, may interact with thyroid cells [9]. The intestinal changes and gut dysbiosis may play a causal role in the development of HT.

Thyroid function has been found to have an impact on the gut microbiota of humans. Virili et al. [9] summarize findings from four papers that describe the microbial composition of 149 patients with HT compared with 73 controls. The authors found varied results on bacterial richness (total number of species), however almost all observed a reduced species diversity. Also, most of the papers found a reduction in the phylum Bacteroidetes and a significant reduction in the genus *Prevotella_9* in two of the papers. The findings indicate that there is an altered gut microbiota associated with HT.

Cayres et al. [10] compared HT patients to controls in terms of stool composition, serum cytokines, zonulin, and dietary habits. They found and significant increase in *Bacteroides* species and a decrease in *Bifidobacterium* species, again, indicating a relationship between microbial composition and HT. In those taking oral levothyroxine, *Lactobacillus* species was decreased compared to those who were not on thyroid replacement indicating that levothyroxine causes changes to the gut microbiome. There was no difference found in cytokines but zonulin, a marker of intestinal permeability, was increased in those with HT, suggesting leaky gut in patients with HT. Based on FFQ, diets were found to be different in HT patients than controls. HT patient diets were significantly different than controls in the following manner: lower in carbohydrates, higher in saturated fats, lower in dairy products, higher in animal protein, lower in fruits and higher in vegetables. This may have an impact on gut microbiome composition. More investigation is need into the clinical, diagnostic, therapeutic and preventative role that this may play.

Biochemical Individuality

As previously discussed, Tregs are known to have important roles in preventing autoimmune conditions, including HT, and variations in the Foxp3 gene may lead to lack of Tregs or Treg dysfunction [8]. A study of 129 HT patients [8] investigated whether two single nucleotide polymorphisms (SNPs) of the Foxp3 gene were associated with the development of HT. They found a significant association with the rs3761548 SNP in those with HT compared to controls suggesting there is an important role for the Foxp3 gene in the pathogenesis of HT.

Deficiency of vitamin D and a variation of the vitamin D receptor (VDR) gene has been linked to autoimmune disorders [11]. Hanna et al. [11] sought to determine if there is a link between the *FokI* and *DsmI* variant of the VDR gene and hypothyroidism as well as to evaluate the impact of different variants on serum 25-OH-vitamin D3 in the subjects. Of the 160 subjects with hypothyroidism included, 112 were due to Hashimoto's Thyroiditis (HT), while 48 others without HT were included as a control. The study found that the *FokI* AA genotype was significantly higher (p=0.02) in the HT group than the control. The 25-OH-D3 levels were also significantly higher (p=0.039) in those with that genotype when compared to all other genotypes. The authors discuss that this elevated level may be due to a receptor dysfunction in which D3 does not function appropriately at higher levels. D3 level was not statistically different between the control group and HT group. This indicates there is a genetic association with HT specific to the *VDR FokI* AA variant in Egyptian adults. While this genotype is likely to have slightly higher 25-OH-D3 levels, the vitamin may not be functioning appropriately due to a vitamin D receptor dysfunction so this must be considered by clinicians. More information is needed on what this means in terms of treatment.

Lifestyle

Genetics is thought to play a major causal role in the pathogenesis of Hashimoto's Thyroiditis (HT), with twin studies pointing to genetic factors accounting for roughly 70% of risk; [12] It is thought that the remaining 30% is due to environmental or lifestyle factors. Specific environmental factors have been shown to induce autoimmune reactions; Wiersinga [13] described factors found to be associated with development of HT (Table 1).

Two nested case-control studies were completed on female subjects looked at alcohol intake and development of HT [12]. Subjects self-reported good health and had no history of thyroid disorders, however had a first- or second-degree relative with documented thyroid disease, either hypo- or hyperthyroidism. They were followed for five years where they had annual blood tests for TSH, free T4, TPO-Ab, and Tg-Ab and completed questionnaires including questions about alcohol intake and smoking status. Study A looked at alcohol intake and de novo development of TPO-Ab as this indicates early stages of HT. Study B looked at alcohol intake and development of overt hypothyroidism

Table 1: Lifestyle factors associated with Hashimoto's Thyroiditis Development [13].

Factor	*Association*
Iodine	Low intake associated with increased prevalence
Smoking	Stopping smoking found to increase risk of TPO or Tg antibodies
Alcohol	Moderate intake found to be preventative
Selenium	Low intake associated with increased prevalence
Vitamin D	Low serum vitamin D levels associated with higher prevalence of TPO antibodies

(TSH < 0.4 mU/l and free T4 >20.1 pmol/l). The results of study A showed that alcohol intake was similar between cases and controls at each point measured. Study B showed that alcohol intake was not different at study entrance but was lower 1 year before onset of overt HT in cases suggesting that alcohol consumption may be protective against developing over HT.

A cross-sectional study looked at the relationship between smoking and thyroid function [14]. They tested thyrotropin levels, a form of TSH, in men and women with known thyroid disease. They found mean thyrotropin level to be lower in both current and former smokers compared with never smokers. In those who previously smoked, thyrotropin gradually increased over time after quitting smoking. This implicates, interestingly, that smoking may provide a protective effect for developing hypothyroidism and that quitting reduces this protection over time. It is not suggested that those at risk for HT should smoke but does suggest a need for research on the mechanism of this relationship.

Energy Dysfunction

The thyroid gland and its hormones play an important role in energy homeostasis as well as cell metabolism. Hypothyroidism has been associated with several chronic diseases including cardiovascular disease, CKD, dementia, fractures and more recently, non-alcoholic fatty liver disease (NAFLD) [15]. NAFLD is a condition with growing prevalence and can result in cirrhosis of the liver and increase risk for hepatocellular carcinoma. It has been suggested that hypothyroidism may play a role in the development of NAFLD. Prevalence of hypothyroidism among those with NAFLD has been reported to be between 15.2 to 36.3%. However, studies that have looked at the correlation between these two have had mixed results.

The authors of a 2017 paper [15] evaluated hypothyroidism and NAFLD's association through a systematic review and meta-analysis. A high correlation (OR=1.52, 95% CI 1.24-1.87, P<0.001) was found between hypothyroidism and NAFLD upon analysis of all 13 included studies. Subsequent analysis and results were as follows: Analysis of six studies of overt hypothyroidism found that it was significantly correlated with NAFLD (OR 1.70, 95% CI 1.23–2.36, P < 0.002). Importantly, no obvious heterogeneity was found amongst these studies. Analysis of nine studies of subclinical hypothyroidism found that it was significantly correlated with NAFLD (OR = 1.40, 95% CI 1.10–1.77, P < 0.006). This led the authors to conclude that there is strong evidence of an association between NAFLD and hypothyroidism and this is present in both those with overt and subclinical hypothyroidism, with the correlation being strongest between those with overt hypothyroidism and NAFLD.

Several mechanisms for the relationship between hypothyroidism and NAFLD have been proposed. One such link includes insulin resistance (IR) and obesity, both of which are involved in the pathogenesis of NAFLD and occur with increased incidence in hypothyroidism [15]. Another link involves the role of thyroid hormones which regulate lipid metabolism. Patients with low levels of thyroid hormones can have increased total cholesterol, LDL cholesterol, and triglycerides which is thought to be due to a reduction in LDL receptors seen with low T4. This increases fatty infiltration in the liver. Another link is that TSH can increase hepatic gluconeogenesis, decrease bile synthesis, and increase cholesterol. Lastly, increased markers of oxidative stress are found in patients with hypothyroidism and oxidative stress is a mechanism of NAFLD. This oxidative stress can cause liver cell injury and insulin resistance by increasing peroxidation of lipids and reducing fatty acid beta-oxidation.

A 2019 trial [16] compared 74 patients with subclinical hypothyroidism (SCH) to controls in terms of CVS risk factors. They measured markers of diabetes and cardiovascular disease including serum insulin, triglycerides, glucose, total cholesterol, LDL cholesterol, HDL cholesterol, and homocysteine. HOMA-IR, an indicator of insulin resistance, was calculated. The authors found total cholesterol and LDL cholesterol to be significantly higher in those with SCH than controls. HOMA-IR and homocysteine were also significantly increased in the SCH group. All of these suggest that patients with SCH have markers conveying increased risk for insulin resistance, diabetes, and cardiovascular disease. However, it must be noted these tests are not diagnostic indicators of the diseases so actual risk for disease cannot be extrapolated from this.

Toxins

There are many substances suspected to be thyroid disruptors and it is thought that these have contributed to the increase in incidence of autoimmune thyroid disorders seen [17]. Researchers have set out to determine whether this exposure to environmental pollutants increases thyroid disease incidence and, indeed, several studies have found that it does. Unfortunately, other studies have found no correlation between the two. The authors of a 2019 study [17] completed on 239 Belgian participants say this conflicting evidence may be explained by poor methodology and flawed statistical analysis amongst the studies previously completed. They performed a case-control study on the associations between mixtures of persistent organic pollutants (POPs) and hypo- and hyperthyroidism to test this.

Serum concentrations of 54 POPs were measured in 35 patients with HT, 44 patients with Grave's disease and 160 controls. These included 16 phenolic organohalogens (POHs), 16 organochlorine pesticides, 7 perfluoroalkyl substances (PFASs), 12 brominated flame retardants (BFRs), and 3 polychlorinated biphenyls (PCBs). The authors used two different approaches to their analysis; One using a monopollutant model, like what had previously been done and a second exploring a multipollutant model. A complex statistical analysis was performed to assess the latter. Nineteen of the POPs studied were found in 40% of the participants so were included in the analysis. They were significantly associated with increased odds of hypothyroidism (OR=98.1, 95% CI: 5.51-1747) with the highest weights attributed to 4 specific POPs: three PCBs (PCB 138, 3-OH-CB 180, and 4-OH-CB 146), and one organochlorine pesticide (4,'4-DDE which is a breakdown product of the more infamous DDT). There was no relationship found between hyperthyroidism and the pollutants.

Another study looked at current-use pesticide exposures, lead, and excess manganese and their effect on T3, T4, and TSH in pregnant women [18]. They measured the participant's urinary pesticide metabolite concentrations of several pesticides as well as hair and blood levels of manganese and blood lead concentrations at study entry and at 10 weeks. Those with higher levels of two pesticides (ethylene thiourea and pyrimethanil) were found to have a lower T4 levels suggesting an association with hypothyroidism. Other pesticides (chlorpyrifos and pyrethroids), blood and hair manganese and blood lead showed hyperthyroidism-like effects (elevated T4, and decreased TSH).

Sleep and Stress

Sleep apnea (SA) has been thought to be correlated with incidence of hypothyroidism based on the findings a several studies [19]. However, other studies have found conflicting information. The studies previously mentioned were limited due to their small size, confounding variables, and methods for categorizing thyroid disorders. Therefore, a group a researchers sought to evaluate the relationship between thyroid

disorders and SA using a larger data set from the National Health and Nutrition Exam Survey (NHANES) as it includes a sleep questionnaire, FT4 and TSH labs, and thyroid medication use.

5,515 participants were included in the analysis. They ultimately found a significant relationship between SA and hypothyroidism. Participants with hypothyroidism had 1.88 times the odds (95% CI, 1.24 to 2.84) of an SA diagnosis than the control group. The authors adjusted for several confounding factors (alcohol, smoking, health care access, insurance status, BMI, demographics, and other comorbidities). They also noted that participants taking thyroid hormones were 2.51 time more likely to have a SA diagnosis than the euthyroid population (95% CI, 1.56 to 4.03). Risk factors for SA in hypothyroid patients includes obesity, macroglossia, upper respiratory tract musculature dysfunction, soft tissue deposition in the upper airway, and decreased ventilatory control. The authors postulate that if these are the methods by which SA develops in the hypothyroid patient, then treating hypothyroidism should improve SA. More information is needed as they describe that the relationship between the two is not fully understood. Their findings do provide more information on the relationship between SA and hypothyroidism and implicate a possible role in screening hypothyroid patients for SA.

Hashimoto's thyroiditis has been linked to inflammation and oxidative stress [20]. T and B lymphocytes are stimulated against TPO and TG which causes increased production of reactive oxygen species (ROS), inflammation of the thyroid gland, and can lead to destruction of thyrocytes. In HT, ROS can also be increased due to a decrease in thyroid hormone levels resulting in a decrease in antioxidant enzymes. A randomized controlled trial looked at the relationship between HT and measures of oxidative stress in HT [20].

Total oxidant status (TOS) and total antioxidant status (TAS) are measures of the oxidant levels in the body. These measures were taken, and Oxidative Stress Index (OSI) was calculated by dividing TOS into TAS. The HT patients were subcategorized into euthyroid, subclinical and overt HT and were compared to controls. Mean TAS levels were lowest in overt HT patients compared to all other groups ($P>0.001$). The mean OSI ($p<0.001$) and TOS ($p<0.006$) were higher in the over HT groups compared to other groups as well. Mean OSI and TAS were similar in euthyroid and subclinical groups but were higher than controls. These results suggest that oxidative stress increases as HT progresses and develops [21].

Conclusion

Hashimoto's thyroiditis is a complex, autoimmune disease that requires a significant workup to identify its root causes and plan effective interventions that treat and/or prevent progression of the disease. Each category in the NIBLETS model is relevant to the condition and must be considered. Genetics and environmental factors play a role in the pathogenesis of HT. Nutrient deficiencies and insufficiencies, inflammation, toxic load, stress, and sleep all have implications for disease progression. It is important to identify and treat factors contributing to the development of HT as without this, irreversible progression of disease can occur. It would be beneficial to focus on early identification and treatment of those with or at higher risk for HT to prevent progression or development of this common condition.

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