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

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Abstract
Hashimoto's thyroiditis (HT) is a chronic autoimmune thyroid disease caused by an interaction between genetic factors and environmental conditions, both of which are yet to be fully understood. The management of HT depends on its clinical manifestations, commonly including diffuse or nodular goiter with euthyroidism, subclinical hypothyroidism and permanent hypothyroidism. However, in most cases of patients with HT, lifelong levothyroxine substitution is required. The additional role of diet for the management of HT is usually overlooked. A literature search regarding the importance and the influence of iodine, selenium, vitamin D and gluten on HT was conducted. In HT careful supplementation of possible deficiencies is recommended for the dietary management of these patients. The use of a diet low in gluten among HT patients with or without celiac disease (CD) is discussed.

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Introduction

Hashimoto's thyroiditis (HT), also called chronic lymphocytic or autoimmune thyroiditis (AITD), is part of the spectrum of chronic autoimmune thyroid diseases and is associated with various degrees of thyroid hypofunction, with thyroid autoantibodies production like the most common, thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab)], and with lymphocytic infiltration [1-5]. Its prevalence depends on age (more frequently appears between 45-55 years), gender (4-10 times more frequent in females than in males) and race (more common in whites than in blacks, hispanics and asians) [3, 6, 7]. Aside from smoking, which decreases the risk for HT, other factors like alcohol, stress, pregnancy and drug use e.g. iodine, interferon-α, immunomodulatory agents such as ipilimumab, pembrolizumab, nivolumab, and the humanised monoclonal antibody to CD52 alemtuzumab may in genetically predisposed individuals, initiate the development of HT [8, 9]. Although the exact mechanism of progressive thyroid tissue destruction is not clear, HT is regarded as a disorder of T cell-mediated immunity, caused by an interaction between susceptibility genes and environ-mental factors, the research of which is still inconclusive [5]. In most cases of patients with HT, lifelong levothyroxine (LT4) substitution, adjusting the dose to achieve normal circulating thyrotropin (TSH) levels, is required [4, 9, 10]. In addition, the coexistence of HT with other organ specific diseases [e.g. pernicious anemia, vitiligo, celiac disease (CD), type 1 diabetes mellitus, autoimmune liver disease, primary biliary cirrhosis, myasthenia gravis, alopecia areata, sclerosis multiplex, Addison's disease], and non-specific [e.g. rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome, systemic sclerosis, mixed connective tissue disease], non-endocrine autoimmune diseases should be evaluated [11, 12]. Nuclear medicine contributes to the diagnosis of HT and hypothyroidism and to differential diagnosis of HT with other diseases. Many of the tests for the evaluation of thyroid gland function and structure and for other diseases coexisting with HT are nuclear medicine tests.

The purpose of this article was to present an update about HT and the impor-tance of iodine, selenium (Se), vitamin D and gluten in autoimmunity of HT and also the role of diet in the clinical course of HT.

Hashimoto's thyroiditis and iodine

Iodine is an essential micronutrient of the diet required for thyroid function and synthesis of thyroid hormones [13]. The recommended adult daily iodine intake is 150μg, increasing to 250μg in pregnancy and lactation [14]. Main diet iodine sources are seafood (e.g. seaweed, scallops, cod, sardines, shrimps, salmon and tuna), animal products (yoghurt, cow's milk, eggs) and fruits (cranberries and strawberries).

Iodine deficiency causes several consequences and manifests with a wide clinical range: from goiter to cretinism [15]. The problem of iodine deficiency in many countries worldwide was solved with iodized salt (IS) programs, and nowadays about two thirds of the world's population (71%) uses IS [16]. In iodine-replete areas, most persons with thyroid disorders have AITD ranging from primary atrophic hypothyroidism, HT to thyrotoxicosis caused by Graves' disease [17]. Other studies revealed the influence of dietary iodine intake on the epidemiology of thyroid dysfunction [17]. Studies on the incidence of AITD have only been conducted in a small number of developed countries. Autoimmune hypothyroidism and thyroid antibodies (TAb) are more common in iodine replete areas than in iodine deficient areas [8, 18]. Hypothyroidism induced by iodine in AITD may be due to a persistent inhibitory effect of iodine on thyroid hormone synthesis and secretion, i.e., a pathologically persistent Wolff-Chaikoff effect [9, 19]. Cases of HT may have inadequate thyroid hormone synthesis, may be unable to escape from the acute Wolf Chaikoff effect, and can develop iodine-induced hypothyroidism. A number of studies indicated that moderate or mild iodine excess (median urinary iodine $\geqslant$220μg per 24 hours) is associated with a more frequent occurrence of hypothyroidism, especially in elderly subjects, the exact mechanism of which has not been clarified [20]. In the longitudinal, population-based DanThyr study [21] subjects were examined at baseline in 1997 to 1998 and re-examined 11 years later in 2008 to 2010 after initiation of a mandatory programme of salt iodization. Even small differences in the level of iodine intake between otherwise com-parable populations were associated with considerable differences in serum TSH at the eleventh year of follow-up [21]. Furthermore, a cross-sectional study from south China showed that high iodine intake was likely to lead to the occurrence of thyroid diseases, such as HT, nodular goiter, and hyperthyroidism, through a long-term process [22].

Even small increases in iodine intake are associated with an increased prevalence of thyroid autoimmunity [15]. Pedersen et al. [23] found an increased prevalence of TAb, 4-5 years after a cautious salt iodization programme, supporting the view that even a small increase in iodine supplementation may be associated with increased thyroid autoimmunity. The underlying mechanism for this association is yet to be elucidated. A recent study [24] suggested that the apoptosis of thyroid follicular cells seen in HT development is likely caused by suppression of autophagy activity, which is induced by iodine excess. This process is mediated through transforming growth factor-β1 downregulation, activation of the Akt/mTOR signaling pathway and enhanced reactive oxygen species (ROS) production. Another potential mechanism could be that iodine excess increases intrathyroid infiltrating Th17 cells and inhibits T regulatory (TREG) cells development, while it triggers an abnormal expression of tumor necrosis factor related apoptosis-inducing ligand (TRAIL) in thyrocytes, thus inducing apoptosis and parenchymal destruction [25]. The fact that excessive iodine plays a significant role in inducing thyroid autoimmunity is also strongly supported in genetically predisposed animals by increasing the immunogenicity of thyroglobulin (TG) [26]. This phenomenon may be explained by the fact that TG is the only self-antigen that undergoes post-translational modification as a consequence of the environmental supply of iodine, with the exposure of previously hidden epitopes [27-31].

Considering the above, high iodine supplementation in HT should be discouraged, as not beneficial and possibly harmful. Discouraging iodine over-supplementation must not preclude its appropriate supplementation in pregnancy to a total intake of 250μg/day [9].

Hashimoto's thyroiditis and selenium

Selenium (Se) is an essential micronutrient of diet with many pleiotropic effects ranging from antioxidant and anti-inflammatory to increasing active thyroid hormone production [32-36]. The thyroid is the organ with the highest Se content per gram of tissue. Among at least 30 selenoproteins, the selenoenzymes such as glutathione peroxidases (GPX), thioredoxin reductases (TR), iodothyronine deiodinases and selenoprotein P, seem to play a unique role in human thyroid function and thyroid hormone homeostasis [2, 32, 33]. Selenium supplementation in patients with AITD, including HT, seems to modify the inflammatory and immune responses, probably by enhancing plasma GPX and TR activity and by decreasing toxic concentrations of hydrogen peroxide (H2O2) and lipid hydroperoxides, resulting from thyroid hormone synthesis [2, 33, 34]. When Se intake is adequate, the intracellular GPX and TR systems protect thyrocyte from these peroxides, as oxidative stress induces TR1 and GPX [4]. This article points out that type 1 and 2 iodothyronine deiodinases (D1 and D2) which support the conversion of peripheral T4 to T3 via outer (5')-ring deiodination of the pro-hormone T4, are selenoproteins and thus this conversion is susceptible to Se deficiency [37]. For that reason Se-deficient individuals have mildly elevated serum T4 and T4 to T3 ratios, but normal TSH [37].

Selenium is present in soil and enters the food chain through plants. So, the Secontent of plants and animals depends on whether the soil where plants grow is seleniferous or not; therefore the amount of Se in the soil is vital. The current recommended dietary intake of Se in adults, in order to achieve the maximal activity of GPX in plasma or in erythrocytes is between 55 and 75μg per day [2, 38-40]. Foods rich in Se are Brazil nuts [40], oysters, tuna, whole-wheat bread, sunflower seeds, most kinds of meat (pork, beef, lamb, turkey,

chicken), mushrooms and rye. In a study conducted in the north-west part of Greece the total daily average intake of Se from the food was 39.3μg per person [41].

Studies have shown different results regarding the efficacy of Se supplementation in HT patients [42-45]. Three meta-analyses have confirmed a suppressive effect of Se supplementationon serum TPO-Ab and Tg-Ab levels in HT patients [42-44]. Particularly, the recently (2016) published systematic review and meta-analysis of Wichman et al. (2016) [44] showed that Se supplementation effectively reduces serum TPO-Ab levels at 3, 6, and 12 months and serum Tg-Ab at 12 months in LT4-treated populations, but not in non treated ones. However, no significant correlation between the baseline serum Se and the decrease in serum TPO-Ab level was demonstrated in LT4-treated patients. This meta-analysis also showed a significant decrease in serum TPO-Ab levels in the patients groups receiving 200μg selenomethionine, but not in those receiving 200μg sodium selenite. The difference might lie on the fact that the absorption of selenite is approximately two-thirds of the absorption of selenomethionine [3, 44]. However, another meta-analysis in the Cochrane library concluded that the evidence to support or refute the efficacy of Se supplementation in patients with HT is insufficient [45].

Inhomogeneity in various groups studied, like differences in the duration of illness, variations in baseline serum Se and/or iodine, the duration of the study and the different Se compounds applied appear to play a role in the divergence of the results [44, 46]. A most recent study from south Italy showed that the 6 months long supplementation with L-selenomethionine had no effect on TPO-Ab [47]. Other Italian [48] and a Greek [2] studies have shown that a 12 months long Se supplementation decreased TPO-Ab. The Greek study also showed that the patients group after ceased receiving Se, after 6 months had a 4.8% increase in the mean serum TPO-Ab concentrations. A recent population-based study in China [49] provided us with potent circumstantial evidence that low Se intake is associated with thyroid autoimmunity because showed that the prevalence of thyroid diseases (except hyperthyroidism, Graves' and nodular disease) was higher in a region of low Se intake (serum Se < 69μg/L) compared to a region of adequate Se intake (serum Se ≥69μg/L) [49].

Previous evidence about the relationship between Se supplementation and type 2 diabetes mellitus (T2DM) has been conflicting [50-54]. In a meta-analysis of five studies (13.460 participants) a significantly higher prevalence of T2DM was confirmed in patients with relatively low (≤97.5μg/L) or high serum Se levels (⩽132.50μg/L), revealing a U-shaped nonlinear dose-response relationship between serum selenium and T2DM [53]. Jablonska et al. (2016) demonstrated that in 76 non-diabetics, daily supplementation with 200μg Se in the form of Se yeast for 6 weeks was associated with a significantly decreased level of HbA1c and hardly affected fasting plasma glucose or down-regulation of seven genes involved in different steps of glucose metabolism (INSR, ADIPOR1, LDH, PDHA, PDHB, MYC, HIF1 inhibitor) [55]. Decreased expression of mRNA levels for these receptors has been linked to insulin resistance and diabetes in humans and animals [56-58].

Chronic ingestion of large quantities of Se may have adverse effects in human health [59-64]. Consumption of approximately 330μg of Se per day could be toxic not only for growth hormones and insulin-like growth factor 1 metabolism but also in the synthesis of thyroid hormones [59, 60]. Possible major side effects include nail and hair loss, anorexia, diarrhea, depression, hemorrhage, liver and kidney necrosis, blindness, ataxia and respiratory disturbances [60, 61]. There have also been instances of dermatitis and CNS disorders in an area with high Se content in Enshi, China [62]. These signs and symptoms of Se toxicity are known as *selenosis.* A Se intake of 50-400μg/d is considered a safe range for adults, while 850-900μg could be allowed as minimum for Se toxicity [65]. In case of Se deficiency, the excessive amounts of H_2O_2 generated lead to immoderate production of T4 and damage of thyroid cells. Selenium deficiency also increases the weight of the thyroid [66] and, combined with iodine deficiency, may lead to a further increase of thyroidal weight. In addition, a phenomenon that has not been studied with sufficient experimental data is that Se deficiency causes accelerated iodine depletion [67]. This may be a protective adaptation against thyroid damage, when Se is deficient and iodine is adequate. Supplementing an HT patient who is deficient in both elements with either Se or iodine would be ineffective and, in certain cases, could cause complications. This explains the deterioration of thyroid function which was observed after Se administration to iodine-deficient people in northern Zaire, a region of endemic goiter, suggesting that the reduction in D1 activity during Se deficiency might be protective against iodine deficiency, presumably by reducing the deiodination of T4, T3, or T3 sulfate [37, 68, 69]. In order to predict whether a patient with HT would benefit from Se supplementation, the clinician should first investigate the patient's iodine status [59]. This is possible by determining the urinary iodine excretion (UIE) test in a 24h urine collection. It should be noted that excessive iodine may indicate dietary excess intake [70], recent contrast media exposure or use of drugs containing iodine (e.g. amiodarone). The effect of iodine-containing antiseptic solutions suggested by healthcare professionals appears to be negligible [71, 72].

In summary, Se supplementation in the form of selenomethionine would be beneficial in HT patients with Se deficiency and adequate iodine intake. Careful Se supplementation is required among HT patients with T2DM, but chronic ingestion of large quantities of Se may have adverse effects in human health.

Hashimoto's thyroiditis and vitamin D

Despite the fact that it was initially described as a "vitamin", vitamin D is now considered as both a fat-soluble vitamin and a steroid hormone that plays a central role in the regulation of calcium/phosphate homeostasis and bone intensity [73]. It is synthesized within the body via two routes: skin exposure to sunlight and dietary intake [5]. The natural sour-

ces that provide humans with large amounts of vitamin D3 are fish (cod liver oil, wild fresh salmon, sardines) and dairy products [5]. Its serum normal range is between 30 and 80ng /mL and levels below 30ng/mL are considered by most scholars indicative of vitamin D insufficiency [5].

Several studies have shown the correlation between vitamin D deficiency and thyroid autoimmunity [5, 74-78], such as the fact that this association applies for all ages [75, 76] and that cholecalciferol supplements are effective in reducing TPO-Ab among HT patients with vitamin D deficiency [78, 79]. What is still unclear, however, is whether the low 25[OH]D levels observed in HT patients are the result of the disease itself or actually part of its cause. Aside from its calcium/phosphate homeostasis functions, vitamin D is considered to be one of the natural immune modulators and a regulator of various immune-mediated processes [5]. The mechanisms underlying the assumption that vitamin D is linked with autoimmunity are not clear but are probably associated with its anti-inflammatory and immunomodulatory functions. The Endocrine Society of USA guidelines affirmed that daily vitamin D intakes of 1500-2000IU are needed to raise the blood level of 25(OH) D constantly above 30ng/mL [80], whilst the Institute of Medicine of USA reported that the tolerable upper intake level, defined as the maximum daily intake above which the potential for adverse health effects may increase after chronic use, is 4000IU per day [81]. Levels of 25(OH) D between 30 and 40ng/mL, that are adequate for avoiding metabolic and autoimmune disorders [82], in more than 97% of the population, can be achieved by an optimal dosage of approximately 2000IU cholecalciferol daily, regardless of increased exposure to UVB [83]. The main side effect of vitamin D overtreatment is hypercalcemia (calcium serum levels above 11mg/dL) and nephrolithiasis. To avoid coronary artery calcification, which is an important predictor of cardiovascular disease (CVD), concomitant use of cholecalciferol with vitamin K2 (menaquinones) may be necessary [84]. Patients with renal disease cannot convert 25[OH]D to active 1,25[OH]D2 and need to receive calcitriol instead of cholecalciferol. In addition, we must consider the potential interactions of some drugs with vitamin D supplements [5, 85]. Apart from cholecalciferol or calcitriol, a regular exposure to sunlight could contribute to the prevention and management of vitamin D deficiency in HT patients. It is obvious that excessive sun exposure and sunburn should be avoided because of the high risk of skin cancer (particularly melanoma) [86].

In summary, the presented data demonstrate the association of vitamin D deficiency with HT pathogenesis, thyroid hypofunction and autoimmunity in general. Taking into consideration the low cost and the minimal side effects of vitamin D supplementation, screening for vitamin D deficiency and careful vitamin D supplementation with monthly monitoring calcium and 25[OH]D levels, when required, may be recommended for patients with HT [5, 73].

Hashimoto's thyroiditis and gluten

Celiac disease (CD) is an immune-mediated disease characterized by chronic inflammation and destruction of the villous structure of the small intestine [87, 88]. It is triggered by the ingestion of gluten, a protein complex found in wheat and related grains, such as barley, rye and oat. Celiac disease has increasingly become considered as a multi-organ disorder, often presenting with diarrhea, malabsorption syndrome and weight loss, and has been linked to a number of diseases including autoimmune disorders [87-90].

According to the international medical bibliography, AITD and CD are clearly associated [12, 90-92]. This might be explained partly by the increased immunosensitivity of CD patients, as part of an autoimmune polyglandular syndrome (APS), by the deficiency of key elements such as Se and iodine due to malabsorption [93, 94] or due to antibodies that affect both target-tissues [95]. According to a most recent meta-analysis, all patients with AITD should be screened for CD, given the increased prevalence of the coexistence of these two disorders [96]. This study advocates that patients with HT must undergo celiac serological tests [serum IgA and IgG gliadin antibodies (AGA-IgA, AGA-IgG), IgA transglutaminase antibodies (TGA), and serum IgA endomysium antibodies (EMA)], and that if any of the celiac serological tests is positive, the patients must be investigated with gastroduodenoscopy and duodenal biopsy [96]. It must be considered that positive thyroid and celiac tests might represent an epiphenomenon, because serum autoantibodies generally do not reflect per se a clinical autoimmune disease [97].

In summary, whereas it is not yet clear whether a gluten-free diet can prevent autoimmune diseases, it is worth mentioning that HT patients with or without CD benefit from a diet low in gluten as far as the progression and the potential disease complications are concerned [98]. Still, a lifelong gluten-free diet is not easy to maintain, it could be very costly and the subject's quality of life may deteriorate [99].

In conclusion, present evidence indicates the beneficial role of diet in the autoimmune status and the clinical course of HT patients. Serum levels of iodine, Se and vitamin D, in HT patients are necessary, and a careful supplementation in case of deficiency of these agents is recommended. Due to the increasing coexistence of HT with CD and other autoimmune diseases, a low gluten diet is important.

The authors declare that they have no conflicts of interest

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