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Role of Vitamin D, Selenium, and Calcarea Carbonica in Management of Hashimoto Thyroiditis

Chean Gaik Chan* and Sairah Abd Karim

Management and Science University, Malaysia

Abstract

Hashimoto Thyroiditis (HT), a form of hypothyroidism, is instances of Autoimmune Thyroid Disease (AITD). HT is the commonest complex chronic autoimmune condition without any iodine deficiency with different degree of thyroid hypofunction. Conventional treatment with levothyroxine has been shown to have side effects, such as drug-induced liver injury. Recently, there has been increasing interest in the use of natural treatment for managing HT. Therefore, this review will concentrate on the viability of natural treatments that is Vitamin D, selenium, and Calcarea Carbonica in symptomatically relieving patients. The findings may help distinguish the common indications in aiding physicians in prescribing natural remedies.

Keywords: Hashimoto thyroiditis; Natural treatment; Vitamin D; Selenium; Calcarea Carbonica.

Introduction

Hashimoto's Thyroiditis (HT), a form of hypothyroidism, additionally called chronic lymphocytic or Autoimmune Thyroiditis (AITD). HT is part of the spectrum of chronic autoimmune thyroid diseases and is related to different degrees of thyroid hypofunction, with thyroid auto-antibodies production, the most common being, Thyroid Peroxidase Antibodies (TPO-Ab) and Thyroglobulin Antibodies (Tg-Ab) [1]. Risk factors for HT include, alcohol, stress, pregnancy, drug use, for example, interferon-immunomodulatory agents such as ipilimumab, pembrolizumab, nivolumab, and the humanized monoclonal antibody to CD52 alemtuzumab, increased iodine intake in genetically predisposed individuals, can initiate the development of HT [1]. There is a genetic component to disease pathogenesis with increased frequency among first degree relatives, and twin studies showing increased concordance in monozygotic compared to dizygotic twins [2].

In HT, the thyroid gland is gradually destroyed resulting in reduced production of thyroid hormones and activating side effects that include fatigue, weight gain, constipation, increased sensitivity to cold, dry skin, depression, muscle aches and diminished exercise tolerance. HT is characterized as a disorder of T cell-mediated immunity, triggered by an interaction between susceptible genes and environmental factors. It is defined by the presence of antibodies to thyroid peroxidase (TPO), the thyroid enzyme that oxidizes iodide ions to iodine for the synthesis of thyroid hormone namely thyroxine T4 and triiodothyronine T3, with lymphocyte infiltration and fibrosis as typical characteristics [3].

Patients with HT have a 1.5-fold increased risk of malignancy of papillary thyroid carcinoma (PTC) and should be monitored [4]. After Rudolf Virchow in 1863 suggested cancer and inflammation are associated and linked with the promotion of malignancy, the proinflammatory autoimmune state of HT has been thought to be a contributing risk factor for cancer. Most of the patients with HT are treated lifelong with levothyroxine. It is crucial to adjust or manage with appropriate weight-based dosing to achieve normal levels of circulating thyroid stimulating hormone (TSH). Levothyroxine has been shown to have alarming side effects. Long term levothyroxine therapy at suppressive doses contributed to secondary osteoporosis. Bone mineral density (BMD) normalized after the patient reduced the dose of levothyroxine and fractures no longer occurred during 23 years of follow up over menopause [4]. Levothyroxine can also contribute to drug-induced liver injury [5]. Due to the safety profile and side effects of levothyroxine, alternative strategies for the management of HT are needed.

To date, several studies have found the role of dietary supplementation for the management of HT especially the use of natural remedies, such as vitamin D, selenium and Calcarea Carbonica [1, 6]. In the present review, we first explain Hashimoto Thyroiditis. Subsequently, this review summarizes the empirical research studies done previously on Vitamin D and Selenium in the treatment for HT and also covers research pertaining homeopathic drug Calcarea Carbonica, exploring relevant information that has not been previously published.

***Correspondence author:** Chean Gaik Chan, Management and Science University, Malaysia, Tel: +60196757714 Email: dgarden.my@gmail.com

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Background of Hashimoto Thyroiditis

Hashimoto Thyroiditis (HT)

Hashimoto Thyroiditis (HT) is inflammation of the endocrine with the thyroid gland, also called autoimmune of chronic lymphocytic thyroiditis. Hakaru Hashimoto, a Japanese physician first described it in 1912 and the disease is named after him [7]. Hashimoto disease is a form of hypothyroidism, happens when there is too little T3 and T4 (thyroid hormones) in the body while excessive thyroid-stimulating hormone (TSH) is built up. Another term for Hashimoto disease is autoimmune thyroiditis. Goitre formation is significant in this form of hypothyroidism due to inflammation [8]. The inflammation is caused by stimulation or activation of CD4 and T-helper cells in the presence of either viral or bacterial infection [9]. The influx of CD4 and T-helper cells as well as activation of other autoantibodies produced by the B helper cells causes destruction of thyroid tissue. Apoptosis is activated by CD8 cells and it is significant in the destruction as well [9]. To help differentiate between Grave's disease and Hashimoto's disease, there is a difference in major histocompatibility complex antigens [8]. Risk factors for HT include underlying genetic-related disorders, increased iodine intake, smoking, and hepatitis C [8]. In HT, the thyroid gland is gradually destroyed resulting in reduced production of thyroid hormones and activating side effects that include fatigue, weight gain, constipation, increased sensitivity to cold, dry skin, depression, muscle aches and diminished exercise tolerance [10].

Epidemiology

Hashimoto's thyroiditis is the most common type of hypothyroidism among Caucasian population especially in North America, relatively lower incidence amongst blacks; with a general prevalence of 10 – 12%. Notably, females possess higher risk compared to males, and higher prevalence in advance age. It was found that in iodine-sufficient region, the occurrence of incidence for female is 350 cases/100,000 per year and male is 60 cases/100,000 per year; lower incidence found in iodine-deficient regions [11]. Interestingly, tobacco smoking can benefits HT as it is able to decrease the level of thyroid autoantibodies and the risk of hypothyroidism.

Hashimoto Thyroiditis in Malaysia

In accordance to study by Jayaram G et al., Indian population exhibited higher prevalence of HT compared to other ethnicities in which the ratio of Malay: Chinese: Indian is 1: 1.2: 2.9. Although Indians constituted only about 7.7% of the Malaysian population, this remarkable finding suggested the underlying genetic, lifestyle and environmental factors that may contribute to the relatively high incidence of HT among this ethnic [12]. In 2016, the Malaysian Endocrine Metabolic Society (MEMS) had initiated MyENDO: Thyroid study to determine the prevalence of thyroid dysfunction, goitre and thyroid nodules in among Malaysian adults. However, the study did not come across the prevalence of HT; instead, this study has given few important information such as the prevalence of thyroid dysfunction is 2.1% (hypothyroidism) and 3.4% (hyperthyroidism) [13].

Understanding Hashimoto Thyroiditis

Anatomy of the Thyroid Gland: The thyroid gland (Greek thyreos, shield plus edios, form) consists of two lobes connected by an isthmus. It is located at the base of the larynx. It is anterior in relation to the neck. Each thyroid gland is embedded with parathyroid glands which are mainly found on their posterior surfaces [10]. This gland is the powerhouse of metabolism in the body to regulate functions of all organs. The thyroid converts iodine and tyrosine into other thyroid hormones. These hormones are called thyroxine (T4) and triiodothyronine (T3).

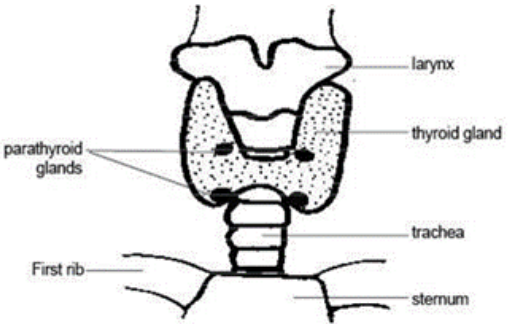

Figure 1. Structure of thyroid glands and tissue surrounding them.

Normal Physiology: In normal hormonal regulation, activity of the thyroid is determined by regulation from the hypothalamus-pituitary-thyroid (HPT) axis, which determines thyroid hormone (TH) production.

However, there is a wide variety of factors that can alternate the expression of components of the HPT axis, including prostaglandins, opioids, arginine-vasopressin, glucagon-like peptide-1, galanine, leptin, glucocorticoids, synthetic analogues of TH, dopamine, gastrin, serotonin, cholecystokinin, gastrin releasing peptide, neuropeptide y, interleukin -1 and -6, tumour necrosis factor alpha, certain drugs, cold, starvation, and illness states [14].The infants recruited for these experiments differed from the normal anthropometric reference (USA, NIH). Recruited infants had a thin arm skinfold up to the seventh year of age and did not increase the skinfold thickness by increased energy intake [3-6]. The increase in energy administration increased BG, insulin resistance, overall inflammation, fecal energy emission and Resting Metabolic Rate but not weight or skinfold thickness in children with relapsing diarrhea. The children were examined at the age of 6-7 years, when they were well [8,9]. Differences in body weight and in height growth in dependence of high energy intake, emerged after the seventh year of life [8,9].

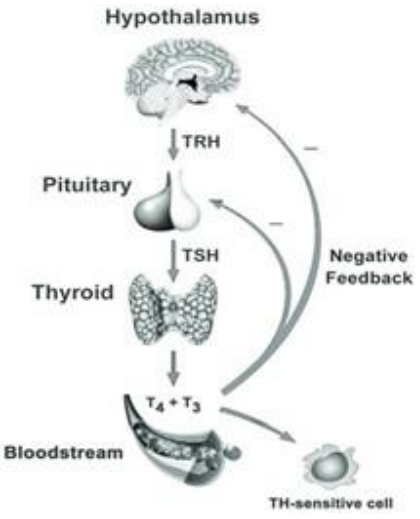

Figure 2. Illustration of Hypothalamic-Pituitary-Thyroid axis and the role of negative inhibition in maintaining physiological control of thyroid hormone levels.

Pathophysiology: Triiodothyronine (T3) and thyroxine (T4) are the essential hormones that regulate metabolism of the body. When the level of these hormones drop, hypothalamus is triggered to produce thyrotropin-releasing hormone (TRH) which may in turn stimulate the anterior pituitary gland to secrete thyroid stimulating hormone (TSH) to subsequently elevate the production of T3 and T4 by the thyroid gland. In normal hormonal regulation, activity of the thyroid is determined by regulation from the hypothalamus-pituitary-thyroid (HPT) axis, which determines thyroid hormone (TH) production. By way of a negative feedback mechanism, TH levels regulate the amount of TRH and TSH secreted. Primary hypothyroidism in the case of Hashimoto's disease, is caused by a deficient production of TH due to the loss of function of the thyroid gland. This leads to a decrease in TH and an increase in TRH and TSH [15].

Studies show several potential mechanisms that contribute to the pathogenesis of Hashimoto's thyroiditis, an autoimmune thyroid disease (AITD). The presence of autoantibodies against thyroid peroxidase (TPOAb) accounts for ninety percent (90%) of patients diagnosed with HT and hence they are utilised to detect the activity of the disease. To date, the severity of the disease does not correlate with the level of anti-TPO antibody present in serum [16]. The thyroid destruction may also occur due to the production of antibodies against thyroid tissue, consequent of the lack of immune tolerance of thyroid cells.

Aetiology and Risk Factors: It is vital to clearly differentiate both aetiology and risk factors in which aetiology refers to the study of causation while risk factors are the determinants associated with the studied disease. The aetiology of HT is poorly understood and there are number of ongoing studies to investigate the causes associated with this disease [10].

One of the most recent study by Singh. G et. al. indicated the association of HT with polyglandular autoimmune syndrome type 2 (PAS-2) which is also known as Schmidt syndrome and Carpenter syndrome, a condition in which the patient may suffer at least two endocrine diseases [17]. Exploring family background in the aspect of genetic heredity has revealed to scientists several genes have strong association with the occurrence of the disease [2] and the findings were confirmed by the twin studies [18]. It was also found that people with Down's syndrome or other chromosomal disorders may have higher chances of getting HT because the presence of autoantibodies might eventually lead to the destruction of thyroid structure [19]. Besides, a study of human herpes virus (HHV) supported the possible association to HT [20]. The occurrence of antibodies such as anti-thyroid peroxidase, antithyroglobulin, antibodies of TSH receptor-blocking have tremendous impact on the destruction of thyroid tissue. However, studies also suggested that a small subset of HT patients does not show positive results of these antibody testing [21, 22]. Other risk factors contribute to the occurrence of HT including gender, with a higher occurrence in females, wherein HT has affected 15% of females worldwide over the past 60 years in comparison to HT affecting 2% of males worldwide in the same timeframe. Additionally, the chances of developing HT also increase with age, particularly with women during menopause, who see a drastic decrease in oestrogen which can affect the thyroid gland's ability to function normally.

Much like other autoimmune diseases, HT may be triggered by bacteria, parasitic, yeast or fungal infections that start within the gastrointestinal tract. In addition to these, excessive iodine levels, radiation exposure (particularly from those undergoing radiotherapy for cancer treatment or from exposure to nuclear events) and environmental or lifestyle factors can also negatively affect the function of the thyroid gland. Furthermore, other autoimmune diseases (AD) such as vitiligo and Celiac disease will also increase the chance of getting HT [1, 23].

Diagnosis: Hashimoto thyroiditis is an autoimmune disease that can be diagnosed based on clinical features, presence of serum antibodies, appearance on thyroid sonogram and thyroid function tests. Clinical features that are commonly reported by hypothyroid patients include constipation, bradycardia, hypertrophic muscles, respiratory abnormalities (bradypnea and hypoxia), anemia, oligomenorrhea, menometrorrhagia, inability to concentrate, memory loss and depression [24]. In fact, most HT patients presented diffuse thyroid enlargement and only about 10% showed atrophic form (without thyroid enlargement).

Antibodies to thyroperoxidase (anti-TPO) and thyroglobulin (anti-TG) are two main serological markers for HT diagnosis. Anti-TPO and anti-TG represents different aspects of autoimmune response against the thyroid gland. For instance, anti-TG reflects innate immune response while anti-TPO reflects adaptive immune response. However, reports show that ten percent (10%) of patients do not have these antibodies [25]. Since the onset of HT is rarely observable in human, higher titers of anti-TPO than anti-TG are commonly found in HT patients [24].

Healthy thyroid gland is composed of various dimensions of thyroid follicles that significantly scatter the ultrasound. However, due to the destroyed thyroid follicles and decrease in thyroid parenchyma, reduced echogenicity is often observed in thyroid sonogram of HT patients [24].

Besides that, thyroid function test can be performed by measuring the serum levels of TSH, free T4 and T3. Elevated level of thyroid stimulating hormone (TSH) while normal to low total or free thyroxine (T4) yielded by thyroid gland are the characteristics of HT. Other signs and symptoms include: dry skin, hoarse voice, feeling cold, heavy and irregular menses, muscle pain, constipation, depression, bradychardia, puffy eyes or face, thinning hair, infertility, memory loss and sluggishness. Elevated level of serum thyroid-stimulating immunoglobulin can be utilised as the indicator of the presence of Graves' disease (GD), another autoimmune disease that causes hyperthyroidism [10, 25].

The Treatment Protocols of Hashimoto Thyroiditis

Conventional Treatment

Presently, thyroid hormone replacement remains as the primary treatment for hypothyroidism caused by Hashimoto Thyroiditis such as levothyroxine (different brand names: Synthroid, Levothroid and Levoxyl) which is administered orally on daily basis. To facilitate the absorption of the agent, one should not be given proton pump inhibitors, iron or calcium supplementation as well as aluminium hydroxide. In most cases, HT patients with manifestation of hypothyroidism may need to continue the treatment for life-long course. The standard dosage of levothyroxine is 1.6 – 1.8 mcg/kg and it could vary in accordance to age, body mass, pregnancy and short-bowel syndrome [17, 26-28]. Levothyroxine can reduce thyroid volume and prevent goiter development in nongoitrous euthyroid children with autoimmune disease. However, the administration of levothyroxine targets the symptoms of HT, instead of the pathogenesis [24].

Natural Treatment

Vitamin D: Vitamin D plays an essential role in regulating bone metabolism, homeostasis of phosphorus and calcium as well as minerals. Vitamin D is a lipid-soluble steroid hormone precursor synthesised as a result of the photochemical reaction of the skin and sunlight or derived from dietary intake of egg and fish oil. Inactive form of Vitamin D needs to be converted to active calcitriol and these conversions require the presence of magnesium (Mg), whereby Mg acts as a cofactor for Vitamin D- binding protein [29]. The activation of cholecalciferol requires two hydroxylation's to take place in liver and kidney, in which the inactive form is converted in the liver to cholecalciferol – 25(OH)D, and then in the kidney to its biologically active form known as calcitriol – 1,25(OH)2D. Serum cholecalciferol level can reflect the nutritional status of the whole body and is used as a marker of Vitamin D saturation [30]. According to Nodehi et al., it might be necessary to use the active form of Vitamin D (calcitriol) instead of cholecalciferol in order to avoid Vitamin D conversion blockage by vitamin D binding protein in immune cells [31]. Vitamin D receptor (VDR) on the cell binds to calcitriol for mediating specific genetic transcription that leads to protein production that may have affected the growth of cells, as well as their differentiation, maturation, and apoptosis.

Evidence has shown the importance of vitamin D in preventing carcinogenesis and autoimmune diseases [32]. Vitamin D can be associated with a number of inflammation and supplementation with Vitamin D is beneficial for the reduction of inflammation [33]. Vitamin D supplementation or thyroid hormones can also be used to regulate the balance between FT4 levels and 25(OH)D [34]. The expression of the nuclear vitamin D receptor (VDR) and the vitamin-D-activating enzyme 1α-hydroxylase (CYP27B1) in most immune cells, including T cells, B cells, and antigen-presenting cells (APCs) including macrophages and dendritic cells (DCs), highlighted the potential involvement of vitamin D in the immune system and in the pathogenesis of autoimmune diseases. The active form of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)2D], inhibits the adaptive immune system by suppressing the proliferation, immunoglobulin production, and differentiation of B cells into plasma cells and promotes the apoptosis of immunoglobulin-producing B cells directly or indirectly mediated by helper T cells. In addition, 1,25(OH)2D has direct regulatory effects on T cell proliferation and cytokine production. 1,25(OH)2D inhibits the proliferation of Th1 cells and the production of Th1 cytokines, such as interferon-gamma, interleukin (IL)-2, and IL-12. 1,25(OH)2D enhances the development of Th2 cells by exerting a direct effect on native CD4+ cells or by acting on APC/DC and thus facilitating the production of Th2 cytokines, such as IL-4, IL-5, and IL-10, which move T differentiation in favour of the Th2 phenotype. 1,25(OH)2D also induces CD4+CD25+ regulatory T cells that produce IL-10, which leads to blocked development of Th1 cells and inhibited secretion of IL-17 by T-effector cells [35].

Vitamin D is often reduced in patients with HT, but lower vitamin D level is not a risk factor for HT [36]. Low Vitamin D level is associated with increased thyroid antibodies level in HT patients and worsen thyroid functions. A placebo-controlled double-blinded randomised clinical trial investigated the impact of 25OH vitamin D therapy in subclinical Hashimoto's thyroiditis in South Asia. They revealed the attainment of normalisation of thyroid function in autoimmune thyroid function in autoimmune thyroiditis among a subset of subclinical hypothyroid patients by using six months of cholecalciferol therapy alone, without the need of hormonal (levothyroxine) supplementation [37].

Generally, recommended upper limit of serum Vitamin D concentration is 50 or 60 ng/mL (125-150 nmol/L) for optimal thyroid function in healthy person and protection from hypothyroidism [38]. In HT patients, it is recommended to keep it at a level higher than 50 ng/mL. Daily supplementation with doses of 3000-5000 IU should allow to obtain and maintain such level. Elevated Vitamin D level increases serum calcium and phosphorus level and as a result may increase calcification of soft tissues (like kidneys and blood vessels). It is generally accepted, that Vitamin D concentration up to 100 ng/mL is safe for both children and adults except those hypersensitive to Vitamin D (those with idiopathic infantile hypercalcemia, Williams-Beuren syndrome, granulomatous disorders and some lymphomas) [29]. A cross- sectional case-control study showed that an increase of each 2 ng/mL of Vitamin D concentration lead to a 1.62-fold reduction in HT risk without the association of Vitamin D concentration with thyroid antibodies or hormones [39]. Another study also demonstrated that each 5 ng/mL increase in Vitamin D level will decrease 19% of the risk of occurrence of HT [40]. Obese adult patients should take 2.5-3 times more Vitamin D than the recommended dose for a normal weight person as the dosage of Vitamin D should be adjusted based on regional or national recommendations with the treatment duration of 1 to 3 months [41].

Numerous studies conducted indicated that the deficiency of vitamin D contribute to the occurrence of autoimmune disease such as multiple sclerosis, Graves' disease, Crohn's disease, inflammatory bowel disease, rheumatoid arthritis and Hashimoto thyroiditis (HT) [42, 43]. The prevalence of Vitamin D insufficiency in HT demonstrated a tendency to be higher in patients with overt or subclinical hypothyroidism than those with euthyroidism [44]. Meta-analysis performed by Wang et al. showed that the development of autoimmune thyroid disease was most likely to occur on individuals with low level of Vitamin D [45].

Investigations have established the relationship between deficiency of vitamin D and thyroid- related autoimmune disease not only in adults but both elderly and children as well [46]. In a study by Kim [35], Vitamin D insufficiency was associated with AITD and HT, especially overt hypothyroidism. Low serum vitamin D levels were independently associated with high serum TSH levels. There is also negative correlation between vitamin D and TSH levels after adjusting for sampling season as well as age, sex and BMI [35]. It was found that in patients with HT, the reduction of anti-thyroid peroxidase can be achieved by the optimum intake of vitamin D. A randomised controlled trial by Chaudhary et. al. showed that vitamin D can help to reduce TPO-Ab, leading to the idea of enhancing HT by giving vitamin D [47], suggesting that Vitamin D could alter the effect of FT4 on autoimmune disease [48]. Another similar study revealed that supplementation with Vitamin D could reduce the level of thyroid antibodies in HT patients and enhance the autoimmune function of the thyroid [49]. A cross-sectional study compared the level of Vitamin D in patients with AITDs, non-AITDs and healthy people showed that Vitamin D deficiency was correlated with the presence of antithyroid antibodies and abnormal thyroid function tests [50].

However, several studies failed to find good correlation between vitamin D and HT [51, 52]. In a study conducted by Anaraki et al., there is no significant effect of Vitamin D on thyroid function and autoimmunity by evaluating the TPO-Ab and TSH levels in vitamin D deficient hypothyroid or euthyroid adult patients with positive TPO-Ab [53]. This result was also reported by Shin et al., which demonstrated negative correlation between Vitamin D level and TPO-Ab levels in patients with AITD [54]. Similar study performed by Ke et al.

revealed that there is no association of FT4 and TSH with vitamin D deficiency in HT patients [55].

A two case-control research in the framework of Amsterdam AITD cohort study determined the association between Vitamin D and early stages of thyroid autoimmunity. Their findings showed higher Vitamin D level in euthyroid participants with genetic susceptibility to AITDs than control group but not any significant differences between patients with newly diagnosed thyroid autoimmunity than the control group. They concluded that Vitamin D is not correlated with early stages of thyroid autoimmunity [56]. Vitamin D treatment in patients with Hashimoto's thyroiditis may slowdown the progression to hypothyroidism and may decrease the risk of cardiovascular diseases [57]. Nevertheless, there is an association between vitamin D intake and thyroid autoimmunity, whether its deficiency contributes is due to the causality link, hence more studies are required to evaluate its validity before any conclusion is to be drawn [58].

Selenium: Thyroid gland is the organ that contains greatest amount of selenium in the form of organic selenium (Se) compound. Se is essential for the synthesis of thyroid hormone and metabolism as well as acts as protective element to prevent thyroid cells from oxidative damage by free radicals.

The human selenoproteome consists of a few selenoproteins and can be classified into housekeeping and stress-related proteins [59]. Selenoenzymes such as glutathione peroxidases (GPX), thioredoxin reductases (TR), iodothyronine deiodinases (DIO) and selenoprotein P were reported to be essential for the homeostasis of thyroid hormone and thyroid action. The main functional proteins in the thyroid gland are GPX and TR, which control the redox status and protect from damage caused by oxygen free radicals by reducing the concentration of hydrogen peroxide and lipid hydroperoxides, thus protecting thyrocyte from oxidative stress [59]. Organic Se compounds (selenomethionine and selenocysteine) have a better absorption rate than inorganic (selenite and selenate). Selenomethionine inhibits production of inflammatory cytokines IFN-γ, TNF-α and IL-2 especially when the treatment is accompanied by levothyroxine (LT4).

However, any destructive inflammatory process is associated with a high level of proinflammatory cytokines that impair selenoprotein biosynthesis [60]. In the event of Se deficiency, serum T4 level is slightly elevated due to the reduction of DIO activity, which plays a role in the conversion of T4 to T3 via outer (5')-ring deiodination of T4 [1]. TPO catalyses the biosynthesis of thyroid hormone and is a major auto-antigen in HT. Hydrogen peroxide (H2O2) is a substrate in catalyzing the iodination and coupling of tyrosyl residues in thyroglobulin to produce thyroid hormone. Furthermore, as a free radical, it is capable of inflicting oxidative damage. Se deficiency contributes to improper function of these two enzymes, thus resulting in ineffective production of T3, inefficient protection against free radicals, and further facilitating cell damage and auto-immune gland destruction [61]. In addition, oxidative stress can occur which decreases suppressor T cells activity and consequently increased IL- 2 production leads to activation of autoreactive T cells and finally to autoantibodies production.

Selenium can be found naturally in our food such as whole grains, meats, seafood, and dairy products and its recommended dietary allowances (RDAs) vary by age and gender [62]. In accordance to the U.S. Food and Nutrition Board, the recommended average RDAs for adults are 55 mcg to 70 mcg. Interestingly, it was noted that the selenium status varies across the human population in the world because of the different selenium content in soil and water [63] and should not be supplemented prior to correction of iodine deficit [64].

Se supplementation may be beneficial to patients with HT, particularly in clinical situations of Se deficiency. A randomized, double-blind, placebo-controlled trial using sodium selenite, pentoxifylline and placebo to treat thyroid disorder, provided evidence that patients with selenium- based agent could acquire better outcome [65]. The baseline Se status of an individual is the most important parameter affecting the outcome of Se supplementation, which might disrupt the self-amplifying cycle of the endocrine-immune system interface and rectify the interaction of lymphocyte with thyroid autoantigens [66]. Toulis et al. showed that different patterns of response to Se supplementation was associated with the baseline aTPO titers in HT that can be used to identify which patients would benefit most from treatment [67]. It is worth to note that non-rare Se deficiency seen in HT patients needs to be replenished with caution due to potentially toxic effects of plasma Se levels >140 μg/L. The therapeutic dose should be addressed individually because some adverse health effects were observed in studies using generally accepted as safe 200 μg of Se daily (alopecia, dermatitis, squamous cell carcinoma, type II diabetes) in non-deficient Se patients. For instance, oral administration of 200 μg Se/day for 3 months effectively decreased serum aTPO titers. Lower supplementation dose (100 μg/day) showed increase in aTPO for 38.1%, while supplementation of 200 μg/day showed decrease of aTPO for 26.2% in the first 6 months [68]. In addition, Se supplementation should be discontinued if plasma Se level is adequate (~125 μg/L) as there is a U-shaped relationship between Se concentration and disease risk [29]. At least 1 year is needed for in-depth assessment of Se treatment in HT and the treatment should be started at an early age to save more thyrocytes, otherwise it may be ineffective in atrophic phase of the pathology [69].

Studies showed a relationship between thyroid functions and the level of selenium in which selenium supplementation might inhibit the occurrence of anti-TPO antibodies. There is a significant reduction of serum aTPO levels during the first 6 months (by 5.6% and 9.9% at 3 and 6 months, respectively) and the continuation of Se supplementation up to 1 year resulted in an additional 8% decrease of aTPO compared with the basal values [70]. A recent meta- analysis by Wichman et al., showed that selenium supplementation reduced serum TPOAb levels both in LT4-treated that untreated patients with chronic autoimmune thyroiditis even if serum TSH improvement remains to be demonstrated [71]. In a study by Manevska et al., a more significant lowering of the aTPO titer from the initial point was found in the hypothyroid patients than euthyroid patients [69]. A double-blind study on the impact of selenium supplementation therapy on the thyroid peroxidase antibody levels and serum oxidative stress in patients with Hashimoto's thyroiditis concluded that selenium supplementation may reduce the level of TPO-Ab titers and oxidative stress in patients with Hashimoto's thyroiditis, especially for those with lower antibody titers (≤200 IU/ml) and short course (≤ 1 year) [72]. Similarly, a study conducted by Zhu et al in 2012 on auto-immune thyroiditis patients with different thyroid functional status revealed that Se supplementation with 200 μg for 6 months resulted in the reduction of aTPO concentration (12.6% in subclinical and 20.4% in the overt form of the disease) [73]. A randomized, placebo-controlled, double-blind study in which euthyroid women with TPOAb ≥ 100 kU/l were randomized to receive 200 μg/day sodium selenite or placebo for 6 months. The treated group showed significant increases in Se and selenoprotein P, with no effect on serum TPOAb, TSH or quality of life [74].

The role of Se supplementation to restore euthyroidism in at least one-third of subclinical hypothyroid patients with auto-immune thyroiditis was observed by Pirola in 2016. Selenium supplementation could normalise the serum levels of TSH in nearly a third of patients with subclinical hypothyroidism due to autoimmune thyroiditis [75]. In 2020, they showed that a short-course supplementation with selenomethionine is associated with a normalization of serum TSH levels which is maintained 6 months after selenium withdrawal, in 50% of the patients with subclinical hypothyroidism due to chronic autoimmune thyroiditis [76].

However, a double-blind placebo-controlled study of approximately 1,000 patients in the United Kingdom revealed no effect of Se supplementation (at 100, 200, or 300 μg/ day) on thyroid function [77]. This was supported by a systematic review indicating unclear evidence to support the efficacy of selenium supplementation in HT patients and hence may not be reliable to help clinical decision making [78].

Vitamin D and Selenium: The concomitant use of Vitamin D and Selenium were reported in several studies. In a study conducted by Krysiak et al., they reported the synergistic effect of Se and Vitamin D on thyroid autoimmunity [49]. For instance, 1α-hydroxylation of Vitamin D to its active form calcitriol was increased by organoselenium resin and the increment of Se uptake by self-reactive T cells was mediated by calcitriol [49]. Furthermore, combination of Vitamin D and selenomethionine could reduce TPOAb and TgAb titres and increase 25-hydroxyvitamin D levels, and in patients with prolactin levels within the reference range (between 10 and 25 ng/mL), there was also reduction in thyrotropin and increase in SPINA-GT in addition to decrease in antibody titres [79].

Homeopathy

Homeopathy (from the Greek όμοιος/homoios, "similar" and πάθος/pathos, "suffering" or "disease") is a science created by Samuel Hahnemann in 1796 resting on three principles. Hahnemann adopted the principle of similia similibus curentur or “like cures like”, first established in the 5th century BC by Hippocrates. The second principle was the principle of individualization. When the remedy profile matches the particular set of symptoms produced by a disease or illness in the patient, the remedy was indicated as the most effective at simulating the vital force to treat the disease. The third principle is the principle of the infinitesimal. Remedies chosen according to this method can be administered in non-toxic weighted doses, but most prescribers use them in dilutions, sometimes very large, which have previously been subjected to very high and very frequent vibrations [19].

Homeopathy treats the patient as a whole (in mental and physical plane together) on symptoms’ similarity. In all the cases, the homeopath avoids suppression because this does not cure but simply pushes problems deeper [80]. There are many ways of homeopathic prescribing. In whatever way the doctor prescribes may be the keynote symptoms approach, miasmatic approach, maybe the reportorial approach, maybe the constitutional approach, maybe past history approach; ultimately they select 1, 2 or 3 main characteristic symptoms representing the keynotes of the medicine. So, in whatever way homeopaths prescribe ultimately it is keynotes approach which gives the easy, confident, quick most practical, effective and viable way of homeopathic practice.

Keynote Symptoms / Remedy Profile: Keynotes in homeopathy are nothing but selection of uncommon characteristic, peculiar signs and symptoms which represent the medicine during prescription. It indicates the identity of the medicine on the basis of which we can individualize and differentiate one medicine from others especially the medicines which are similar in the sphere of action and manifestation [81]. So, the keynote symptoms of Calcarea Carbonica is best suited to shy, fair, disposed to grow fat, flabby who become easily obese, fatigued and are slow in their movements. Heavy sweating from the scalp is also found in both adults and children, more specifically from the back and neck – this manifestation in what is known as “wet pillow”. There may also be an aversion to meat, dairy foods and coffee, while simultaneously craving for sweets, eggs or indigestible things such as chalk or soap [82]. They are also prone to constipation and sensitive to the cold. Coldness: general; of single parts in youth. Girls who are fleshy, plethoric, being the keynote of its action. Symptoms are ameliorated during dry weather. Other symptoms include backache, enlarged and hard glandular swellings (Goiter), scrofulous, rachitic condition, arthritic condition, inflammatory joint pain (i.e tennis elbow), difficulty swallowing, indigestion with flatulence, bloating, sour belching or constipation generally offer numerous opportunities for the exhibition of Calcarea Carbonica. Difficulty in swallowing, painless hoarseness; worse in the morning. Great debility sensation as if the throat was contractile once swallowing. These symptoms were found in patient with hypothyroidism, pituitary and thyroid dysfunction [83].

Mental / Mind Symptoms: The mental symptoms in homeopathic prescribing are given special importance. As we know that diseases originate in the vital molecular processes, obviously, mental and physical symptoms whether subjective or objective are the expressions of these molecular errors. This striking symptom helps in finding out the right remedy for easy cure [80].

Anxiety may be due to irrational fears, typically due to darkness, illness, death or failure. These ailments are commonly associated with those who overwork themselves or over-exhaust themselves. Characteristics of these individuals include those who are hard-working, capable, conscientious people who take on too much responsibility and find their symptoms worsen when they are over-worked. Their lives are all about completing a task-list and they find themselves unable to relax and work to exhaustion, until they must give up their task altogether [82].

Miasm: The word miasm means a cloud or fog in the being. The theory suggests that if 100% of all disease is miasmatic, then 85% is due to the primary and atavistic miasm Hahnemann called Psora. The remaining 15% of all disease he held to be either syphilitic or sycotic, being derived from suppressed Syphilis or suppressed Gonorrhoea. The theory of miasms originates in Hahnemann's book The Chronic Diseases which was published in 1828, around the same time that he decided to fix 30c as the standard potency for all homoeopaths. The three miasms, Psora, Syphilis, Sycosis in that work are held to be responsible for all disease of a chronic nature and to form the foundation or basis for all disease in general [84].

Treatments with Calcarea Carbonica: Calcarea Carbonica, or more commonly referred to as carbonate of lime or Calcarea ostrearum was proved and published by Hahnemann in his Chronic Diseases (1821-34) as one of several calcium salts used in homeopathy. Calcium is required by the human body to function efficiently, since various essential compounds are produced when it combines with protein in the body. The homeopathic remedy is derived from oyster shells and the calcified remains of similar crustaceans. This compound also occurs naturally in chalk, marble, pearls, limestone and coral [82].

A few studies have shown that Calcarea Carbonica could

improve the immune response against tumor cells [85, 86]. In addition, Calcarea Carbonica was hypothesized to be able to induce apoptosis in tumor cells by activating the host's immune system and inducing apoptosis via immunomodulatory circuit [87]. Furthermore, Calcarea Carbonica was demonstrated to promote complete cysts removal from polycystic ovarian syndrome [88]. Besides that, in a study by Chauhan et al., 11 out of 16 children with subclinical hypothyroidism with or without autoimmune thyroiditis treated with Calcarea Carbonica have significant reduction in TSH and antiTPOab titres [89].

In a clinical study of 30 cases, 10 cases (33.33%) were prescribed Calcarea Carbonica based on their maism. The cases were studied for a period of 6 months. According to the study 86.66% of the cases were females, 56.66% housewives with past history of acute infectious disease. This led to awakening of slumbering psora. Marked improvement in the TSH, considerable decrease in BMI, Antimiasmatic treatment is effective [90].

Conclusions

This review has shown the potential use of Vitamin D, selenium and Calcarea Carbonica on management of HT. For Vitamin D, several studies have shown that optimum intake of Vitamin D can help to reduce TPO-Ab levels in HT patients, slowing down the progression to hypothyroidism and enhancing the autoimmune function of thyroid. As selenium is an essential component for the synthesis of thyroid hormone and metabolism, supplementation with selenium could also help to lower the TPO-Ab levels, as well as reduce oxidative stress in HT patients. The homeopathic remedy, Calcarea Carbonica, could also aid in the reduction of TPO-Ab and serum TSH level. However, there are not many research articles providing insight on the synergistic use of Vitamin D, selenium and Calcarea Carbonica in HT treatment. Therefore, further studies focusing on the combination effect are needed to determine the effectiveness of this combination in symptomatically relieving patients with HT.

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Conflicts of Interest

The authors declare no conflict of interest.

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