Hashimoto's autoimmune thyroiditis and vitamin D deficiency. Current aspects

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 not yet completely understood. The significant association between vitamin D deficiency and HT has been investigated regarding the immune role of this hormone. In HT, an immunologic reaction is triggered when thyrocytes express major histocompatibility complex (MHC) class II surface HLA-DR antigens, a process induced by the production from T helper (Th)1 type lymphocytes, of inflammatory cytokines (especially IFN-γ), which may be inhibited by 1,25[OH]2D. Genetic polymorphism of vitamin D receptor (VDR), binding protein (DBP) and of a 1α-hydroxylase (CYP1α) may also predispose to the development of HT. Considering current evidence, presented in this review, screening for vitamin D deficiency and careful vitamin D supplementation, when required, may be recommended for patients with HT. Further research is needed in patients with HT in order to investigate the mechanisms by which vitamin D affects autoimmunity and also to evaluate the cost-effectiveness of vitamin D supplementation and to suggest the possible optimal dose treatment.

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Introduction

Although initially described as a "vitamin", vitamin D is now considered a hormone, known, first of all, for its role in regulation of calcium-phosphate homeostasis. It is known that vitamin D has multiple functions in humans, including functions acting as an immunomodulatory factor and thus, may play a role in the pathogenesis of HT, as will be discussed in this article.

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Hashimoto's thyroiditis and vitamin D

Hashimoto's thyroiditis (HT), also called chronic lymphocytic or autoimmune thyroiditis, is part of the spectrum of chronic autoimmune thyroid diseases (AITD) [1, 2]. It is characterized by female preponderance, enlargement of the thyroid gland, thyroid autoantibody production and lymphocytic infiltration, associated with various degrees of thyroid hypofunction [1-6]. 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, e.g., cytotoxic T-lymphocyte associated-4 (CTLA-4), human leukocyte antigen (HLA), TSH receptor (TSHR) and environmental factors, both of which are not yet completely understood [6-10]. The contribution of nuclear medicine to diagnosis and differential diagnosis of HT is remarkable. The scintigraphic findings in HT using ^{99m}Tc-pertechnetate or iodine-131 are highly variable mimicking several thyroid disorders including diffuse hyperplasia, nodular goiter, cold nodules, and rarely hot nodules [11]. Measurements of serum concentration of TSH, total and free thyroxine (T4) and tri-iodo-thyronine (T3), antithyroid per-oxidase (anti-TPO), antimicrosomal (anti-TM) or antithyroglobulin (anti-Tg) antibodies are more accurate than the enzyme-linked immunosorbent assay (ELISA) tests when performed with radioimmunoassays (RIA) or immunoradiometric assays (IRMA). Studies indicate that TPO is the major component of thyroid microsomal antigen recognized by autoantibodies [12]. Indirect immunofluorescence (IF) tests, are also specific methods for the determination of autoantibodies against TPO and Tg and for HT [13].

Vitamin D metabolism is quite complex. In order to better follow its relation to HT, some interesting points of vitamin D metabolism will be reminded. Vitamin D is a fat-soluble prohormone which is synthesized within our body via two roots: exposure of

the skin to sunlight and a small part from our diet [14-17]. Solar ultraviolet B radiation (wavelength, 290-315nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin D3, which is then rapidly converted to vitamin D3. Dietary vitamin D3 comes from natural sources such as wild fresh salmon, cod liver oil or milk. Vitamin D2 is manufactured through the ultraviolet irradiation of ergosterol from yeast. Both D2 and D3 are used as vitamin D supplements [14]. Vitamin D made in the skin (D3) or ingested (either as D2 or as D3) is carried in the bloodstream bound to DBP and undergoes, in the liver, hydroxylation to 25-hydroxyvitamin D3 (25[OH]D or calcidiol) [14-17]. This is the major circulating form of vitamin D and the one measured by clinical laboratories to determine the vitamin D status [17]. 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 [6, 14, 18]. However, vitamin 25[OH]D is inactive and must be converted in the kidneys to 1,25-dihydroxy vitamin D3 (1,25[OH]2D or calcitriol), the biologically active form. The conversion to 1,25[OH]2D is catalyzed by parathyroid hormone (PTH), and therefore in states of vitamin D deficiency, low levels of 25[OH]D are found, while the 1,25[OH]2D levels are either normal or actually slightly elevated, because the excess of PTH that is stimulated by the low 25[OH]D levels stimulates the conversion of 25[OH]D to 1,25[OH]2D. So, patients with vitamin D deficiency usually have a low serum 25[OH]D level, a high PTH level, a low normal serum calcium, and a normal or an elevated serum 1,25[OH]2D level. The biologically active form of vitamin D, 1,25[OH]2D, regulates numerous functions in various cell types, through binding to a nuclear high-affinity receptor (vitamin D receptor, VDR) in complex with the 9-cis-retinoic acid receptor on both calcemic and non-calcemic tissues (as the intestine, bones, kidneys, elements of the haematopoietic and immune systems, liver, endocrine glands, etc.) [16, 19-21].

Serum levels of vitamin D are influenced by numerous factors, including mainly sun exposure, skin pigmentation, age, adiposity, physical activity, drugs, and dietary intake [6, 16]. Vitamin D is known, first of all, for its role in the regulation of calcium-phosphate homeostasis, and its deficiency is traditionally known to cause osteomalacia [22]. The association of vitamin D nutritional deficiency with other conditions, such as obesity, bariatric surgery, diabetes mellitus, cardiovascular disease, malignancy and several systemic and organ-specific autoimmune diseases has been lately documented [6, 19, 20, 22-25]. Finally, there are numerous problems in regularly measuring serum vitamin D levels in order to assess its possible deficiency [26].

Several studies have revealed low serum 25[OH]D levels in patients with HT indicating an association between vitamin D deficiency and thyroid autoimmunity [6, 9, 14, 27]. However, it is unclear if the low 25[OH]D levels observed in HT are the result of the autoimmune disease process or part of its cause. In a recent study [6], the prevalence of vitamin D deficiency (serum 25[OH]D lower than 10ng/mL) was significantly higher in patients with AITD compared with healthy controls (72% versus 30.6%; P<0.001), as well as in patients with HT compared to patients with non-AITD (79% versus 52%; P<0.05). Low levels of vitamin D were also related to the presence of antithyroid antibodies and abnormal thyroid function tests [6], suggesting the involvement of vitamin D in the pathogenesis of AITD. In another study [14], the prevalence of low vitamin D levels (serum 25[OH]D lower than 30ng/mL) in HT cases (148 of 161, 92%) was significantly higher than that observed in healthy controls (102 of 162 controls, 63%; P<0.0001). Bozkurt et al. (2013) recently demonstrated that serum 25[OH]D levels of HT patients were significantly lower than of controls, and the severity of 25[OH]D deficiency was correlated with the duration of HT, thyroid volume, and antibody levels [27]. Other reports have yielded conflicting results (weak or no association between low vitamin D levels and thyroid autoimmunity) [28, 29].

Does vitamin D play a role in the pathogenesis of HT?

Vitamin D is considered one of the natural immune modulators and a regulator of various immune-mediated processes [19]. The mechanisms underlying the assumption that vitamin D is linked with autoimmunity are not clear but probably are associated with its anti-inflammatory and immunomodulatory functions [6, 8, 9, 14]. Most of the known biological effects of vitamin D are mediated through the VDR, and can be regulated by the DBP and the CYP1α [6, 16], while several genetic studies have demonstrated an association between thyroid autoimmunity susceptibility and genetic polymorphisms of the VDR, DBP and CYP1α which reduce the biologic activity of vitamin D [6, 8, 9, 27, 30-33]. The immune modulator properties of vitamin D are ascribed to its effect on cells of the innate and adaptive systems, including macrophages, dendritic cells (DC), and T and B lymphocytes, all of which possess both the enzyme CYP1α and VDR [34, 35]. The DC are antigen-presenting cells originating from bone marrow and also a primary target for the immunomodulatory activity of vitamin D. After undergoing antigenic maturation, DC secrete IL-12 and present the processed antigen on their surface and in association with the major histocompatibility complex (MHC) class II, to other cells of the immune system (i.e. T cells). In addition, 1,25[OH]2D has direct immunomodulatory effects at the level of the T cell VDR [9, 14, 35, 36]. Together, these immunomodulatory effects can lead to the protection of target tissues, such as thyroid cells in autoimmune diseases, considering that in HT, a disorder of T cell-mediated immunity, immunologic attack is triggered when thyrocytes express MHC class II surface HLA-DR antigens, a process induced by the production of Th1 type inflammatory cytokines (especially IFN-γ) [14]. Moreover, at another stage, after being activated by T cells, B cells' ongoing proliferation might be inhibited and apoptosis might be induced by 1,25[OH]2D. Thus, 1,25[OH]2D might decrease antibodies that react with thyroid antigens [14]. This evidence suggests a model in which the effectiveness of 1,25[OH]2D treatment of AITD will result from the inhibition of the development and function of Th1 cells and induction of other T cells, including Th2 cells. The exact levels of vitamin D that are sufficient to improve the immune regulatory function and lead to an effective immune response, should be investigated.

Low vitamin D levels in autoimmune diseases can be ex-

plained by malabsorption (e.g., inflammatory bowel diseases or systemic sclerosis), or by lack of sun exposure due to skin involvement or photosensitivity, or by reduced outdoor activity and chronic corticosteroid treatment [6]. Although the majority of patients with thyroid disease do not suffer from significant skin diseases, malabsorption or reduced outdoor activity, several HT patients have a comorbid autoimmune disorder, or thyroid hypofunction, or other causes which could affect the production, absorption and utilization of vitamin D [37-39].

Is vitamin D supplementation recommended for HT patients?

Vitamin D supplementation has been characterized as beneficial for the primary prevention and management of some autoimmune diseases in humans [6, 19]. However, the beneficial role of vitamin D supplementation in AITD has been demonstrated only in animal models [40, 41]. Considering the presented data about the association of vitamin D deficiency with HT pathogenesis, and the low cost and minimal side effects of vitamin D supplementation, screening for vitamin D deficiency and careful vitamin D supplementation with monthly monitoring of calcium and 25[OH]D levels, when required, may be recommended for patients with HT. However, this recommendation is not included in the Endocrine Society's clinical practice guidelines [6, 18], possibly due to limited related studies.

The main side effect of vitamin D treatment is overtreatment leading to hypercalcemia (calcium serum levels above 11mg/dL). Patients with renal disease cannot convert 25[OH]D to active 1,25[OH]2D and need to receive calcitriol instead of cholecalciferol. In addition, we must consider the potential for some drugs to vitamin D supplementation interactions [42].

In conclusion, present evidence indicates a possible role of vitamin D in the immunological pathogenesis of HT. However, screening for vitamin D deficiency and vitamin D supplementation among HT patients is not yet applied. The mechanisms by which vitamin D affects autoimmunity, the cost-effectiveness of vitamin D supplementation in patients with HT, as well as its optimal safe doses should be further investigated.

The authors declare that they have no conflicts of interest.

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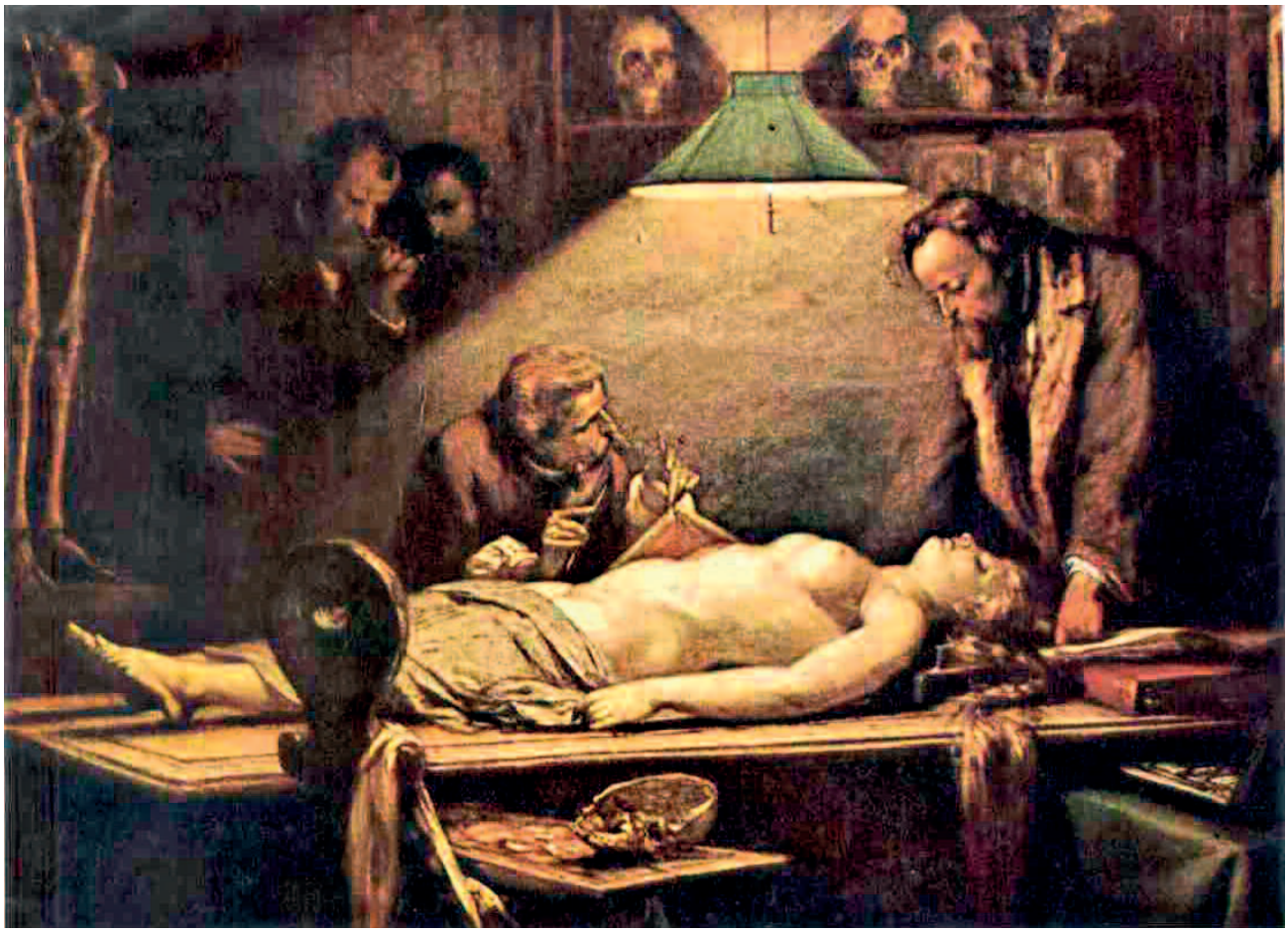

Anatomy of a beautiful lady from Frankfurt (1864-66), by Hasselhorst. The artist is at the back of the picture smoking.