VitD3 and Autoimmune Thyroiditis

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Active 1,25$(OH)_2$ D3 is generated in immune cells via 1-α-hydroxylase, subsequently interacting with the VitD3 receptor to promote transcriptional and epigenomic responses in the same or adjacent cells. Despite considerable progress in deciphering the role of VitD3 in autoimmunity, its exact pathogenetic involvement remains to be elucidated.

Keywords: vitamin D ; autoimmune thyroiditis ; antithyroid peroxidase antibodies

1. VitD3 and the Epidemiology of Autoimmune Thyroiditis

One of the first studies in humans was carried out by Kivity S et al. in 2011: the authors observed that VitD3 deficiency was significantly higher in autoimmune thyroid disease (AITD) patients compared to healthy individuals (72% vs. 30.6%; $p < 0.001$) [1]; they also noted a correlation between deficient VitD3 status, antithyroid peroxidase antibody (TPOAb), and abnormal thyroid function tests ($p = 0.059$). One year later, however, Efraimidis G. et al. conducted (A) a cross-sectional study comparing euthyroid subjects with genetic susceptibility for AITD, though without thyroid antibodies, with controls, while also carrying out (B) a longitudinal study comparing patients who had developed de novo thyroid antibodies with those who had not [2]. In neither group were the early stages of thyroid autoimmunity (in study A genetic susceptibility and in study B development of TPOAb) associated with low VitD3 levels.

VitD3 deficiency has been associated with AITD, particularly in premenopausal women with HT [3][4], with several recent trials providing good evidence of a bidirectional association.

A recent epidemiological survey with 1812 participants conducted in Tianjin, China, showed, by logistic regression analysis, that TPOAb positivity was associated with 25(OH)D3 deficiency (odds ratio (OR): 2.428, 95% confidence interval (CI): 1.383–4.261) and 25(OH)D3 inadequacy (OR: 1.198, 95% CO: 0.828–1.733; $p = 0.008$) [5].

In 2015, two cross-sectional case-control studies by the same group, including 70 patients each with newly diagnosed HT and GD, were carried out, while a nested case–control study was conducted in which the levels of 25(OH)D3 were compared between 610 women who developed PPT during the follow-up after delivery and those who did not [6]. In none of these studies did the serum 25(OH)D3 levels reveal any association with TPOAb or with antithyroglobulin antibody (TgAB) nor was any association found with the subjects' levels of thyroid hormones or with thyroid-stimulating hormone (TSH) in GD and HT. Importantly, however, it was noted that the lower the VitD3 level is, the higher the risk of developing AITD was. Also of interest was the finding that with each 5 nmol/L increase in serum 25(OH)D3 concentration, a fold reduction was observed, with a 1.55, 1.62, and 1.51 increase in GD, HT, and PPT risk, respectively [6].

In an analysis of six clinical trials including 258 patients with HT, a significant difference was found between the 25(OH)D3 levels in the HT group when compared with those of the control group (95% CI: 12.43, 25.58, $p < 0.001$) [7]. Moreover, the combined results of the analysis indicated that VitD3 supplementation may significantly reduce TPOAb titers. It is, however, noteworthy that no significant association was observed between VitD3 serum levels and those of TgAB, TSH, free triiodothyronine (FT3), and free thyroxine (FT4), suggesting that VitD does not affect thyroid function in patients with HT [7].

In contrast, in another study in which 5230 patients were enrolled, 25(OH)D3 levels were higher in the non-HT group than in the HT group [8]. Multiple regression analysis demonstrated that HT was statistically significantly correlated with male gender, body mass index (BMI), waist circumference, TSH, and FT3 and FT4 levels in the insufficiency group and deficiency group. An increase of 25(OH)D3 by 1 ng/mL at the normal reference level was reported to correspond to an increase of 2.78 ng/dl in FT4 concentration and a decrease of 0.17 mIU/L in TSH [8]. Meanwhile, TSH was negatively correlated with 25(OH)D3 concentrations, while FT3 and FT4 levels were observed to be positively correlated with 25(OH)D3 levels.

A possible association between low VitD3 levels and HT was studied in 261 healthy overweight and obese subjects (200 women and 61 men) [9]. VitD3 deficiency was found in 55% of all subjects (144/261), 17% of whom (45/261) had HT. The percentage of subjects with VitD3 deficiency was significantly higher among those with HT (31/45, 69%) compared to those without HT (113/216, 52%) (p = 0.042). The study results strongly pointed to VitD3 deficiency being significantly related to HT in overweight and obese individuals, thus confirming previous findings that obesity is associated with lower VitD3 circulating levels [9]. Hence, obese patients with VitD3 deficiency should be checked for the possible presence of HT.

In line with the latter observations, it was demonstrated that long-standing HT patients on levothyroxine (LT4) treatment had far lower 25(OH)D3 levels (11.4 ± 5.2 ng/mL) compared to newly diagnosed HT subjects (13.1 ± 5.9 ng/mL, p = 0.002) and control subjects (15.4 ± 6.8 ng/mL, p < 0.001) [10]. Serum 25(OH)D3 levels were inversely correlated with TgAB levels (r = −0.335, p < 0.001). The severity of the 25(OH)D3 deficient state correlated with the duration of HT, thyroid volume, and antibody levels, indicating a potential role of VitD3 in the development of HT and/or its progression to hypothyroidism.

In the Survey on Prevalence in East China for Metabolic Diseases and Risk Factors (SPECT-China) cross-sectional study, which was performed in 23 sites in East China and included 10,636 participants, four 25(OH)D3-related and four TPOAb-associated single nucleotide polymorphisms (SNPs) were genotyped, and their genetic risk scores were estimated (GRS) [11]. Bidirectional Mendelian randomization (MR) analysis was performed, which showed a significant association of GRS with 25(OH)D3 (B −0.093, 95% CI −0.111 to −0.074) and TPOAb level (B 0.067, 95% CI 0.002 to 0.132). TPOAb GRS was significantly associated with TPOAb concentration (B 0.345, 95% CI 0.135 to 0.556), but not with 25(OH)D (B −0.030, 95% CI −0.091 to 0.030). By applying 25(OH)D3 GRS in the MR analysis, a causal relationship between genetically determined 25(OH)D3 and increased TPOAb concentration was detected. A higher VitD3 GRS was associated with a higher risk of TPOAb positivity, supporting a causal association between decreased VitD3 and increased concentration of TPOAb in the study population [11]. These results provide some evidence that VitD3 supplementation may lessen AITDs susceptibility; if the findings are confirmed, they will be of considerable benefit to public health, considering the wide prevalence of VitD3 deficiency.

VitD3 levels, as well as rates of VitD3 deficiency, were compared between 461 HT cases and 176 controls drawn from a Croatian Biobank of HT patients (CROHT) [12]. HT patients were additionally divided into two groups, mild and overt, in order to take into account HT severity. Although no significant differences in VitD3 levels or rates of VitD3 deficiency were detected between HT patients and controls, a clearly significant difference was observed between mild and overt subgroups for VitD3 levels (OR = 1.038, p = 0.023). These data may suggest that prolonging VitD3 deficiency may advance hypothyroidism.

Concerning GD, an experimental study conducted by Misharian et al. [13] investigating the relationship between VitD and autoimmunity made an unexpected finding: VitD3-deficient BALB/c (albino, laboratory-bred strain) mice developed persistent hyperthyroidism following immunization with the TSH receptor, while the sufficient VitD3 group did not. It was these unanticipated results that led to the hypothesis that low VitD3 levels may contribute to the development of AITD.

A cross-sectional study was carried out in 2013, recruiting 54 patients with GD, of whom 18 were in remission (R) and 36 in non-remission (NR), and 49 controls (C) [14]. The authors reported that serum 25(OH)D3 levels were significantly lower in the NR group than in the R and C groups (14.5 ± 2.9 vs. 18.2 ± 5.1 ng/mL, p < 0.005, and 18.6 ± 5.3 ng/mL, p < 0.0005, respectively) [14]. However, they found no significant association between serum 25(OH)D3 levels and TSH receptor antibodies (TRAb) levels in NR. Based on the above results, any association of VitD3 with disease severity appears to be unlikely.

In 2018, a study compared VitD3 levels in 292 patients with newly diagnosed GD and in 2305 controls, while in 708 patients and 1178 controls, SNPs in the *VDR*, *DBP*, and *CYP27B1 receptor* genes were examined to determine whether there was any association with GD and/or Graves' ophthalmopathy (GO) [15]. The investigators observed, by performing a genetic analysis, that two single SNPs in *VDR*, namely that *rs10735810* (OR = 1.36, 95% CI: 1.02–1.36, p = 0.02) and *rs1544410* (OR = 1.47, 95% CI: 1.03–1.47, p = 0.02) were indeed associated with GD. Meanwhile, no difference was observed in the mean VitD3 levels between genotypes in either *rs10735810* or *rs154410* carriers.

The existing data appears to point to a higher prevalence of VitD3 deficiency in patients with GD. However, the role of VitD3 in GD is still an unresolved issue, as the association does not necessarily imply a causal relationship [16].

2. Effects of VitD3 Treatment on Hashimoto's Thyroiditis and Graves' Disease

A case-control study enrolled 218 subjects and supplemented them with cholecalciferol over a period of 4 months. [17]. The results revealed, firstly, that there was a significant negative correlation only between serum 25(OH)D3 levels and TPOAb and, secondly, that TPOAb levels were significantly higher in 186 of the subjects who had HT together with VitD3 deficiency compared to 32 HT patients with no VitD3 deficiency (364 ± 181 IU/mL vs. 115.8 ± 37.1 IU/mL, $p < 0.0001$). Cholecalciferol supplementation in the 186 VitD3-deficient patients led to a significant decrease, by 20.3%, in serum TPOAb titers. At the conclusion of the 4-month study period, BMI, serum TGAB, and TSH levels had decreased by 2.2%, 5.3%, and 4%, respectively, though no significance was achieved.

A double-blind, randomized, placebo-controlled clinical trial enrolling 56 VitD3-deficient euthyroid or hypothyroid patients with positive TPOAb studied the effects of VitD3 treatment over a 12-week period [18]. The subjects were randomly allocated to two groups, numbering 33 and 32 participants, which received oral VitD3 (50,000 IU weekly) ("VitD-treated group") and a placebo ("placebo group"), respectively. The mean (standard error) of VitD increased significantly in the VitD3-treated group (45.53 (1.84) ng/mL vs. 12.76 (0.74) ng/mL, $p = 0.001$). No improvement was noted in any metabolic parameter following 12 weeks of high-dose VitD3 supplementation in the HT patients with a VitD3 deficiency [18].

In 2019, a study was carried out to ascertain whether VitD3 supplementation was able to modify the circulating thyroid autoantibodies and thyroid profile in female patients with HT [19]. Forty-two women with HT were enrolled and randomly assigned to two groups: a VitD3 group receiving 50,000 IU VitD3 and a placebo group receiving placebo pearls, taken weekly for a period of 3 months [19]. Although a significant decrease in TgAb and TSH was observed in the VitD3-treated group, there was no noteworthy reduction of TPOAb in this group compared to the placebo group nor was there any significant change in the thyroid hormone concentrations in the VitD3-treated group.

It may, thus, be concluded that short-term high-dose VitD3 supplementation may be capable of reducing HT activity, albeit further confirmation of the latter results should be obtained via large randomized controlled trials.

In GD, a double-blinded clinical trial was set out to investigate the effects of VitD3 supplementation on the muscle weakness and quality of life (QoL) impairments that are frequently observed in GD patients [20]. Patients were randomized to VitD3 70 µg (2800 IU)/day or a matching placebo as an add-on to standard antithyroid drug (ATD) treatment at baseline and during a period of 3 and 9 months of follow-up. Whereas VitD3 supplementation in fact decreased muscle strength and did not improve QoL, the ATD treatment normalized muscle function and improved lean body mass [20].

In an analysis to study the association between VitD3 deficiency and HT and GD, 11 case-control studies that included 1952 AITD patients with HT or GD were reviewed [21]. The majority of the studies analyzed revealed that HT and GD patients have a greater prevalence of VitD3 deficiency or low serum 25(OH)D3 levels. Other studies, however, failed to establish an association between VitD3 deficiency and HT and GD [21].

In patients with GD, it is advisable to routinely measure serum VitD3 concentrations, particularly in smokers and in those with increased titers of thyrotropin receptor autoantibodies (TRAb) and/or with GO. If VitD3 deficiency is registered, low-dose VitD3 supplementation should be administered [22]. While VitD3 has a remarkable ability to modulate both innate and adaptive immune responses, since VitD3 deficiency is associated with increased autoimmunity incidence and susceptibility to infection, it must be supplemented cautiously. Given that taking high VitD3 supplementation over a long period of time can induce hypercalcemia, a moderate dose, i.e., 10 micrograms a day, is advised for most people [23][24], and monitoring of calcium levels, particularly in older patients, is recommended [24].

3. VitD3 and Pregnancy

VitD3 deficiency in pregnancy has been associated with pre-eclampsia, preterm delivery, gestational diabetes mellitus, and small-for-gestational-age births and is a risk factor for AITD, although a causative relationship in the development of AIT has not to date been clearly demonstrated [25]. The modulation of immune responses by $1,25(OH)_2D3$ consolidates T regulatory cells (Tregs) function, while inhibiting inflammatory responses of Th17 cells, which may reduce the risk of unexplained recurrent spontaneous abortion.

In a retrospective cross-sectional study of 133 women with repeated spontaneous abortions before 20 weeks, gestation serum VitD3 levels were measured, and autoimmune parameters were monitored [26]. It was observed that 63 of the women (47.4%) had low VitD (<30 ng/mL) and that the prevalence of antiphospholipid antibody (APA) in the low VitD group (VDlow) was significantly higher (39.7%) than in the group with normal VitD levels (VDnl) (22.9%) ($p < 0.05$). It was

also noted that prevalence of antinuclear antigen antibody (VDlow vs. VDnl; 23.8 vs. 10.0%, OR 2.81, 95% CI 1.1–7.4), anti-ssDNA (19.0 vs. 5.7%, OR 3.76, 95% CI 1.1–12.4), and TPOAb (33.3 vs. 15.7%, OR 2.68, 95% CI 1.2–6.1) was significantly higher in the VDlow group than in the VDnl group. However, no difference in Th1/Th2 ratios between the VDlow and VDnl groups was found [26].

In another study, serum samples of 50 women were selected retrospectively, and VitD3 levels were measured at gestational weeks 8, 20, and 32 [27]. The median 25(OH)D3 levels were lower in the first trimester (28.29 nmol/L) than in the second (39.23 nmol/L) or third (40.03) trimester. Only triiodothyronine was associated with VitD3 in the first trimester (p = 0.024), with only a statistically significant trend detected (p = 0.063). No association was observed between VitD3 and any other thyroid parameters [27]. Although large studies are needed, the data pointed to adequate dietary supplementation during the entire period of pregnancy, particularly for those with autoimmune diseases and women in the first trimester.

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