The Role of Vitamin D in Thyroid Diseases

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Abstract: The main role of vitamin D is regulating bone metabolism and calcium and phosphorus homeostasis. Over the past few decades, the importance of vitamin D in non-skeletal actions has been studied, including the role of vitamin D in autoimmune diseases, metabolic syndromes, cardiovascular disease, cancers, and all-cause mortality. Recent evidence has demonstrated an association between low vitamin D status and autoimmune thyroid diseases such as Hashimoto’s thyroiditis and Graves’ disease, and impaired vitamin D signaling has been reported in thyroid cancers. This review will focus on recent data on the possible role of vitamin D in thyroid diseases, including autoimmune thyroid diseases and thyroid cancers.

Keywords: autoimmune thyroid disease; Graves’ disease; Hashimoto’s thyroiditis; thyroid cancer; vitamin D

1. Introduction

Vitamin D is a steroid molecule, mainly produced in the skin, which regulates the expression of a large number of genes [1]. The vitamin D receptor (VDR) is found in most tissues and cells in the body. The main role of vitamin D is regulating bone metabolism and calcium and phosphorus homeostasis. Recent evidence suggests that vitamin D deficiency, which is common worldwide, could also have non-skeletal actions including an important role in autoimmune diseases, cancers, metabolic syndromes, cardiovascular disease, and infection, as well as all-cause mortality [1–3]. Low levels of vitamin D have also been associated with autoimmune thyroid diseases (AITD) such as Hashimoto’s thyroiditis (HT) and Graves’ disease (GD). Impaired vitamin D signaling has been reported to encourage thyroid tumorigenesis [4–6].

The aim of this review is to summarize recent data on the possible association between vitamin D and thyroid diseases, including AITD and thyroid cancers.

This review is based on an electronic search of literature in the PubMed database published from January 2002 up to May 2017 using combinations of the following keywords: vitamin D or vitamin D deficiency/insufficiency and autoimmune thyroid disease, Hashimoto’s thyroiditis, Graves’ disease, thyroid cancer, or thyroid nodule. The references included in previously published review articles were also scanned, and any relevant papers were also included.

2. Vitamin D Sources, Metabolism, and Action

There are two forms of vitamin D, vitamin D3 (or cholecalciferol) and vitamin D2 (or ergocalciferol). The former is mainly synthesized in the skin by 7-dehydrocholesterol reductase upon exposure to ultraviolet B (UVB) radiation, and can be also obtained from a few dietary sources (mainly fatty fish), while the latter is produced by plants and fungi [7,8].

Both forms of vitamin D are transported to the liver where they are converted to 25-hydroxyvitamin D (25(OH)D or calcidiol) by 25-hydroxylase (CYP27A1 and CYP2R1). 25(OH)D is...
the major circulating and stored form of vitamin D, and the serum levels of this form are considered the best marker to measure whole body vitamin D status [5,7–9]. Although debated, vitamin D deficiency is usually defined as 25(OH)D level < 50 nmol/L, and vitamin D insufficiency as 50–75 nmol/L of 25(OH)D [1,2,10]. At physiological concentrations, 25(OH)D is biologically inactive and must be converted to the biologically active form 1,25-dihydroxyvitamin D (1,25(OH)_{2}D or calcitriol) by 1α-hydroxylase (CYP27B1) in the kidneys. The activity of the 1α-hydroxylase enzyme is under strict control by parathyroid hormone (PTH), and is inhibited by high levels of 1,25(OH)_{2}D and fibroblast growth factor 23 (FGF23). In addition, 1,25(OH)_{2}D is inactivated by 24-hydroxylase (CYP24A1) [5,7–9]. However, other cell types, including immune cells, also express 1α-hydroxylase and are able to convert the inactive 25(OH)D into the active 1,25(OH)_{2}D in either an autocrine or paracrine manner without the above feedback regulation [8]. It has been proposed that serum 25(OH)D levels serve as the main determining factor of extrarenal 1,25(OH)_{2}D synthesis. Indeed, numerous associations have been found between vitamin D status (reflected by serum 25(OH)D concentration) and extraskeletal health outcomes, rather than with serum 1,25(OH)_{2}D concentrations [5]. Vitamin D can be stored in and released from fat cells, and it is bound to the vitamin D binding protein (DBP). Approximately 88% of 25(OH)D and 85% of 1,25(OH)_{2}D is bound by DBP, and 12–15% of circulating vitamin D is bound to albumin, with the free form having greater accessibility to target cells [5].

The active 1,25(OH)_{2}D form binds to the nuclear vitamin D receptor (VDR), which acts on the vitamin D response element (VDRE) of target genes to exert its effects [5]. Directly and indirectly, 1,25(OH)_{2}D controls the expression of over 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis [2]. Among others, the brain, prostate, breast, and colon tissues, as well as immune cells, all express VDR and respond to 1,25(OH)_{2}D. 1,25(OH)_{2}D decreases the cellular proliferation of both normal cells and cancer cells and induces their terminal differentiation, in addition to being a potent immunomodulator [2]. A membrane-bound VDR may also exist, which would mediate more immediate, non-genomic actions of 1,25(OH)_{2}D [9].

Recently, several genetic studies have demonstrated that an individual’s susceptibility to autoimmune disorders and cancers is associated with polymorphisms in numerous proteins and enzymes associated with vitamin D function, including VDR, DBP, CYP27B1, CYP2R1, and CYP24A1. Four single-nucleotide polymorphic (SNP) variants of the VDR gene (ApaI, BsmI, FokI, and TaqI) are most frequently studied [5,11].

3. Vitamin D and Autoimmune Thyroid Diseases

3.1. Mechanisms

Autoimmune thyroid diseases, including HT and GD, are the most common organ-specific autoimmune disorders [12]. These AITDs are polygenic diseases resulting from a combination of genetic predisposition (thyroid-specific genes and immune-modulating genes) and environmental triggers (iodine, selenium, drugs, irradiation, smoking, infections, stress, etc.), characterized by lymphocytic infiltration into the thyroid gland and production of thyroid-specific autoantibodies [12,13]. Chronic autoimmune thyroiditis, or HT, is a typical T-cell-mediated autoimmune disease characterized by a diffuse goiter, the presence of anti-thyroid peroxidase (anti-TPO) and/or anti-thyroglobulin (anti-Tg) antibodies in serum, varying degree of thyroid hypofunction, and intrathyroidal infiltration of B and T lymphocytes with CD4^{+} type 1 T helper (Th1) subtype predominance. In GD, lymphocytic infiltration is mild and involves mainly CD4^{+} type 2 T helper (Th2) cells, which induce the production of antibodies to bind to the thyroid stimulating hormone (TSH) receptor. This stimulates the growth and function of thyroid follicular cells leading to hyperthyroidism, indicating a humoral immune response [12]. In summary, in genetically predisposed individuals, the disruption of these immune-endocrine interactions by environmental factors is able to shift the balance between Th1-Th2 immune response. This results in a Th1-cell-mediated autoimmune reaction with thyrocyte destruction and hypothyroidism in HT, but in a hyperreactive
Th2-mediated humoral response against TSH receptor (TSHR) with stimulatory antibodies leading to hyperthyroidism in GD [12].

Vitamin D plays a significant role in modulation of the immune system, enhancing the innate immune response while exerting an inhibitory action on the adaptive immune system [7,11]. Most immune cells, including T cells, B cells, and antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages, express VDR and 1α-hydroxylase [7,8,14]. At the level of the APCs, 1,25(OH)₂D inhibits the surface expression of major histocompatibility complex class II antigens and co-stimulatory molecules, and prevents the differentiation and maturation of DCs as well as their activation and survival, leading to decreased antigen presentation and T cell activation. Moreover, 1,25(OH)₂D also modulates DC-derived cytokine expression by inhibiting the production of interleukin (IL)-12 and IL-23 (major cytokines driving Th1 differentiation and IL-17 producing T helper (Th17) cell differentiation, respectively) and enhancing the release of IL-10. Thereby, 1,25(OH)₂D indirectly shifts the polarization of T cells from a Th1 and Th17 phenotype towards a Th2 phenotype [14,15]. In addition, 1,25(OH)₂D directly leads to a shift from a pro-inflammatory to a more tolerogenic immune status, which includes diverse effects on T cell subtypes. 1,25(OH)₂D inhibits Th1 cell proliferation, differentiation, and production of cytokines (IL-2 and interferon-γ), as well as Th17-derived cytokines (IL-17 and IL-21), but also promotes the production of anti-inflammatory Th2 cytokines (IL-3, IL-4, IL-5, and IL-10), shifting the balance from a Th1 and Th17 phenotype to a Th2 cell phenotype. 1,25(OH)₂D favors regulatory T cell (Treg) cell development via modulation of DCs and by directly targeting T cells, thereby blocking Th1 development. Finally, 1,25(OH)₂D inhibits B cell proliferation and differentiation into plasma cells, immunoglobulin secretion (IgG and IgM), memory B cell generation, and also induces B cell apoptosis [7,8,11,14–16]. The ability of 1,25(OH)₂D to suppress the adaptive immune system promotes immune tolerance and appears to be beneficial for a number of autoimmune disease [7,8].

3.2. Animal Studies

The administration of 1,25(OH)₂D in addition to cyclosporine was demonstrated to effectively prevent the induction of experimental autoimmune thyroiditis (EAT) with a synergistic effect in CBA mice [17,18]. In another study using an EAT model in Wistar rats, 1,25(OH)₂D prevented and ameliorated the pathological changes of the thyroid gland and corrected thyroid autoantibody production and the cytokine disequilibrium [19]. In addition, vitamin D-deficient BALB/c mice developed persistent hyperthyroidism after immunization with TSHR, not seen in vitamin D-sufficient mice [20].

3.3. Human Studies

Several clinical studies have reported a low vitamin D status in AITD or HT, indicating an association between vitamin D deficiency and thyroid autoimmunity (Table 1) [21–34]. Kivity et al., reported that the prevalence of vitamin D deficiency (25(OH)D level < 25 nmol/L) was significantly higher in 50 patients with AITD compared with 98 healthy individuals (72% vs. 30.6%; p < 0.001) as well as in 28 patients with HT compared to 42 patients with non-AITD (79% vs. 52%; p < 0.05). Vitamin D deficiency was also found to be correlated with the presence of anti-thyroid antibodies (p = 0.01), suggesting the involvement of vitamin D in the pathogenesis of AITD [21]. Tamer et al., demonstrated that the prevalence of vitamin D insufficiency (25(OH)D level < 75 nmol/L) in 161 HT cases was significantly higher than in 162 healthy controls (92% vs. 63%; p < 0.0001). Among the HT cases, the prevalence of vitamin D insufficiency tended to be higher in patients with overt hypothyroidism (47/50, 94%) or subclinical hypothyroidism (44/45, 98%) than in those with euthyroidism (57/66, 86%), although the differences were not statistically significant [22]. Bozkurt et al., revealed that serum 25(OH)D levels of HT patients (180 treated and 180 non-treated) were significantly lower than 180 controls, and that the severity of vitamin D deficiency was correlated with the duration of HT, thyroid volume, and antibody levels, suggesting a potential role of vitamin D in the development of
HT and/or its progression to hypothyroidism [23]. By comparing 41 hypothyroid HT patients with 45 healthy euthyroid individuals, Mansournia et al., found a significant inverse association between serum 25(OH)D levels and HT (OR 0.81, 95% CI 0.68–0.96; \(p = 0.018\)), such that each 12.5 nmol/L increase in serum 25(OH)D level resulted in a 19% decrease in the odds of HT [24]. Shin et al., reported that 111 patients with elevated anti-thyroid antibodies had lower levels of serum 25(OH)D\(_3\) than 193 patients with no elevation (\(p < 0.001\)). Moreover, after adjusting for age, sex, and body mass index (BMI), a negative correlation (\(r = -0.252\); \(p < 0.001\)) was found between 25(OH)D\(_3\) and anti-TPO levels in a group of individuals with AITD [25]. Unal et al., demonstrated that 254 newly diagnosed HT and 27 GD patients had lower 25(OH)D levels than 124 healthy controls (\(p < 0.001\)), and serum 25(OH)D levels were inversely correlated with anti-Tg (\(r = -0.136\); \(p = 0.025\)) and anti-TPO (\(r = -0.176\); \(p = 0.003\)) antibodies [26]. Choi et al., analyzed 6685 subjects who underwent routine health checkups and found significantly lower serum 25(OH)D levels in pre-menopausal women with AITD, but not in postmenopausal women. Vitamin D deficiency (<25 nmol/L) and insufficiency (25–75 nmol/L) were significantly associated with AITD only in pre-menopausal women, suggesting a possible link between vitamin D and estrogen in the development of AITD [27]. In a population-based health survey including 1714 Chinese adults, Wang et al., also showed a negative correlation (\(r = -0.121\); \(p = 0.014\)) between 25(OH)D and anti-Tg levels, but only in female subjects [28]. Recently, the author reported that the prevalence of vitamin D insufficiency (25(OH)D level < 75 nmol/L) was significantly higher in 369 AITD patients (221 HT and 148 GD) than in 407 non-AITD patients (\(p = 0.011\)), and was higher in HT patients than in those with GD or non-AITD (\(p = 0.017\)). In addition, among the HT cases, patients with overt hypothyroidism had a higher prevalence of vitamin D insufficiency (\(p < 0.001\)) and lower 25(OH)D levels (\(p = 0.009\)) compared with HT patients with euthyroidism and subclinical hypothyroidism or patients without AITD. Serum 25(OH)D levels were significantly negatively correlated with serum TSH levels after adjustment for age, sex, BMI, and sampling season (\(r = -0.127\); \(p = 0.013\)) [29]. A recent meta-analysis of 20 case-control studies showed that AITD patients have lower 25(OH)D levels and are more likely to be vitamin D deficient compared to controls [30]. Subgroup analyses showed that GD and HT patients also have lower 25(OH)D levels and are more likely to be deficient in vitamin D. The criterion for vitamin D deficiency in the studies included in this meta-analysis was a 25(OH)D level of <25–50 nmol/L [30]. Muscogiuri et al., studied 168 elderly subjects (mean age of 82 years) and showed a significantly higher prevalence of AITD in subjects with vitamin D deficiency (25(OH)D level < 50 nmol/L) (\(p = 0.002\)) and a significant correlation between 25(OH)D and anti-TPO levels (\(r = -0.27\); \(p = 0.03\)) [31].
Table 1. Clinical studies for an association between vitamin D status and autoimmune thyroid diseases.

| Sources                          | Study Subjects                                                                 | Low Vitamin D Status (25(OH)D Level (nmol/L)) | Notable Findings                                                                 |
|----------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------|
| Kivity et al., 2011 [21]         | 50 AITD (28 HT, 22 GD), 42 non-AITD, 98 healthy controls                      | <25                                           | 70% of HT, 64% of GD, 52% of non-AITD patients, 30% of controls (SD)            |
| Tamer et al., 2011 [22]          | 161 HT, 162 healthy controls                                                 | <75                                           | 91.9% of HT, 63% of controls (SD)                                                |
| Bozkurt et al., 2013 [23]        | 180 euthyroid HT, 180 newly diagnosed HT, 180 healthy controls                | <25                                           | 48.3% vs. 35% vs. 20.5% of each groups (SD); correlated with thyroid volume ($r = 0.15$), anti-TPO ($r = -0.36$), anti-Tg levels ($r = -0.34$) (SD) |
| Mansournia et al., 2014 [24]     | 41 hypothyroid HT, 45 healthy controls                                       | NA                                            | inverse association with HT (OR 0.81 for 12.5 nmol/L increase in 25(OH)D) (SD)  |
| Shin et al., 2014 [25]           | 111 AITD, 193 non-AITD patients                                               | NA                                            | 31.5 nmol/L in AITD, 36.2 nmol/L in non-AITD (SD); negative correlation between 25(OH)D and anti-TPO levels ($r = -0.252$) (SD) |
| Unal et al., 2014 [26]           | 254 newly diagnosed HT, 27 GD, 124 healthy controls                           | NA                                            | 37.2 vs. 48.4 vs. 56.2 nmol/L in each groups (SD); correlated with anti-Tg ($r = -0.14$), anti-TPO levels ($r = -0.18$) (SD) |
| Choi et al., 2014 [27]           | 673 anti-TPO (+), 6012 anti-TPO (−) subjects for routine health checkups     | <25 (D)                                       | 50.7 nmol/L in anti-TPO (+), 56.4 nmol/L in anti-TPO (−) in premenopausal women (SD); anti-TPO (+) 21.2%, 15.5%, and 12.6% in D, I, S groups in premenopausal women (SD); OR 1.95 for TPO-Ab (+) (SD) |
| Wang et al., 2015 [28]           | 1714 subjects for population-based health survey                             | NA                                            | correlation ($r = -0.12$) between 25(OH)D and anti-Tg levels only in female subjects (SD) |
| Kim, 2016 [29]                   | 369 AITD (221 HT, 148 GD), 407 non-AITD patients                              | <75                                           | 46.1% of AITD, 48.9% of HT, 41.9% of GD, 37.1% of non-AITD (SD); lower vitamin D status in overt hypothyroid HT than other HT groups or non-AITD (SD) |
| Muscogiuri et al., 2016 [31]     | 168 elderly subjects                                                         | <50 (D)                                       | prevalence of AIT 28% vs. 8% in D and non-D groups (SD); correlation between 25(OH)D and anti-TPO levels ($r = -0.27$) (SD) |
| Camuradan et al., 2012 [32]      | 152 children (78 recently diagnosed HT, 74 controls)                          | <32.5                                         | 73.1% of HT, 17.6% of controls (SD); 31.2 vs. 57.9 nmol/L (SD); inverse correlation with anti-TPO levels ($r = -0.30$) (SD) |
| Evliyaoglu et al., 2015 [33]     | 169 Turkish children (90 HT, 79 healthy controls)                             | <50                                           | 71.1% of HT, 51.9% of controls (SD); 41.6 vs. 52.4 nmol/L (SD); OR 2.28 for HT risk in 25(OH)D <50 nmol/L |
| Sources                          | Study Subjects                                                                 | Low Vitamin D Status (25(OH)D Level (nmol/L)) | Notable Findings                                                                                                                                 |
|---------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Metwalley et al., 2016 [34]     | 112 Egyptian children (56 AIT, 56 healthy, age- and sex-matched controls   | <12.5 (DD)                                    | vitamin D deficiency rate 71.4% of AIT, 21.4% of controls (SD); 16.2 vs. 33.9 nmol/L (SD); negative correlations between 25(OH)D and disease duration, anti-TPO, anti-Tg, and TSH (r = −0.676, −0.533, −0.487, −0.445, respectively) (SD) |
| Goswami et al., 2009 [35]       | 642 students, teachers and staff aged 16–60 years                           | <25                                           | no association with anti-TPO positivity; weak inverse correlation between 25(OH)D and anti-TPO levels (r = −0.08)                                  |
| Effraimidis et al., 2012 [36]   | 803 subjects from the Amsterdam AITD cohort                                   | NA                                            | no association with early stages of thyroid autoimmunity                                                                                 |
| D’Aurizio et al., 2015 [11]     | 100 AITD (52 HT, 48 GD), 126 healthy controls                                | <50 nmol/L                                    | no difference                                                                                                                                |
| Yasmeh et al., 2016 [37]        | 97 HT, 88 healthy controls                                                   | <50 (D)                                       | no association between HT and vitamin D deficiency; S 51.7% of HT vs. 31.1% controls in females (SD); 76.8 vs. 68.8 nmol/L in HT and control females (SD); correlation between 25(OH)D and anti-TPO levels (r = 0.436) in males (SD) |
| Yasuda et al., 2012 [38]        | 72 females (26 new onset GD, healthy controls)                              | <37.5 nmol/L                                  | 65.4% of GD, 32.4% of controls (SD); 35.9 vs. 42.7 nmol/L (SD); correlation between 25(OH)D and thyroid volume (r = −0.45) (SD)               |
| Yasuda et al., 2013 [39]        | 103 females (36 non-remission GD, 18 remission GD, 49 controls)             | NA                                            | 36.2 vs. 45.4 vs. 46.4 nmol/L (SD)                                                                                                           |
| Zhang et al., 2015 [40]         | 70 GD, 70 controls                                                           | <50 nmol/L                                    | higher vitamin D deficiency rates and lower 25(OH)D levels in anti-TSHR (+) GD than anti-TSHR (−) GD or controls (SD); inverse correlation between 25(OH)D and anti-TSHR levels in anti-TSHR (+) GD |

25(OH)D, 25-hydroxyvitamin D; AITD, autoimmune thyroid disease; HT, Hashimoto’s thyroiditis; GD, Graves’ disease; SD, significant difference; anti-TPO, anti-thyroid peroxidase antibody; anti-Tg, anti-thyroglobulin antibody; NA, not available; OR, odds ratio; D, deficient; I, insufficient; S, sufficient; AIT, autoimmune thyroiditis; DD: severely deficient; TSH, thyroid stimulating hormone; anti-TSHR, anti-TSH receptor antibody.
A few studies have focused on investigating the correlation between low vitamin D status and HT in children. Camurdan et al., observed higher rates of vitamin D deficiency (25(OH)D level < 37.5 nmol/L; 73.1% vs. 17.6%; \( p < 0.0001 \)) and lower 25(OH)D levels (31.2 vs. 57.9 nmol/L; \( p < 0.001 \)) in 78 children with recently diagnosed HT compared with 74 controls, and an inverse correlation between 25(OH)D and anti-TPO levels \( (r = -0.30; \ p = 0.007) \) [32]. Evliyaoglu et al., studied 90 children with HT and 79 age-matched healthy controls. The prevalence of vitamin D deficiency (25(OH)D level < 50 nmol/L) in HT patients was significantly higher than in the control group (71.1% vs. 51.9%; \( p = 0.025 \)). The mean serum 25(OH)D3 level in the HT group was significantly lower compared to the control group (41.6 vs. 52.4 nmol/L; \( p = 0.001 \)), and HT was observed 2.28 times more frequently in individuals with 25(OH)D levels of <50 nmol/L (OR 2.28, 95% CI 1.21–4.3) [33]. Metwalley et al., investigated 56 children with autoimmune thyroiditis (AIT) and 56 healthy controls and reported similar results, including a higher rate of vitamin D deficiency (71.4% vs. 21.4%; \( p < 0.001 \)) and lower 25(OH)D levels (16.2 vs. 33.9 nmol/L; \( p < 0.001 \)) in the AIT group compared to the controls. The difference was more evident in patients with overt hypothyroidism than those with subclinical hypothyroidism (9.5 vs. 16.4 nmol/L; \( p < 0.01 \)). In addition, there were significant negative correlations between serum 25(OH)D and patient age, disease duration, BMI, and levels of anti-TPO, anti-Tg and TSH (\( p < 0.001 \) each). The authors proposed that low serum vitamin D is significantly associated with AIT, but is not an independent risk factor for the progression of AIT to overt hypothyroidism [34].

Of note, a few studies that have evaluated whether vitamin D supplementation is beneficial for AITD or HT have been published recently. Mazokopakis et al., showed that serum 25(OH)D levels in 218 euthyroid HT patients were inversely correlated with anti-TPO levels. Anti-TPO levels were also significantly higher in vitamin D-deficient HT patients (25(OH)D level < 75 nmol/L) compared to HT patients with no vitamin D deficiency. After 4 months of oral vitamin D3 supplementation (1200–4000 IU/day) in 186 vitamin D-deficient patients, there was a significant decrease (20.3%) in serum anti-TPO levels [41]. Chaudhary et al., analyzed 100 newly diagnosed AITD patients and found that anti-TPO levels were highest among patients in the lowest 25(OH)D quartile (\( p = 0.084 \)). At the 3-month follow-up, there was a significant fall in anti-TPO levels in patients that received vitamin D3 supplementation at 60,000 IU per week for 8 weeks when compared to patients without vitamin D supplementation (−46.73% vs. −16.6%; \( p = 0.028 \)). The number of responders (≥25% fall in anti-TPO level) was higher in the group that received vitamin D supplementation (68% vs. 44%; \( p = 0.015 \)) [42]. Simsek et al., demonstrated that anti-TPO and anti-Tg levels in AITD patients with a 25(OH)D level <50 nmol/L were significantly decreased as a result of administration of vitamin D at 1000 IU/day for 1 month (\( p = 0.02 \) and \( p = 0.03 \), respectively) [43].

Some studies, however, have failed to find an association between low vitamin D status and AITD or HT. Goswami et al., revealed no association of vitamin D deficiency (<25 nmol/L) and anti-TPO positivity, but only a weak inverse correlation between serum 25(OH)D and anti-TPO levels in 642 students, teachers, and staff from India \( (r = -0.08; \ p = 0.04) \) [35]. A total of 803 subjects from an AITD cohort from Amsterdam were investigated in a longitudinal study by Effraimidis et al., who showed that 25(OH)D levels were not lower in AIRD cases compared to controls, nor in subjects with a genetic susceptibility for AITD or seroconverters with de novo occurrence of anti-TPO antibodies. The authors concluded that vitamin D deficiency is not associated with the early stages of thyroid autoimmunity [36]. D’Aurizio et al., also reported no differences in vitamin D deficiency (<25 nmol/L) and 25(OH)D levels between 100 AITD patients (52 HT and 48 GD) and 126 healthy controls [11]. In contrast to the above results, Yasmeh et al., investigated 97 HT patients and 88 healthy controls and reported a higher 25(OH)D level and higher rate of vitamin D sufficiency (>75 nmol/L) in HT females relative to control females, but there were no differences in males. A significant positive correlation between 25(OH)D and anti-TPO levels was observed in males \( (r = 0.436; \ p = 0.016) \). The authors pointed out that HT was not associated with higher rates of vitamin D deficiency relative to the control group [37].
A relationship between vitamin D and GD has also been reported. In a study by Kivity et al., the prevalence of vitamin D deficiency in GD was found to be higher than in controls, but was not significantly different compared to that in non-AITD patients [21]. Other authors have reported that vitamin D levels are no lower in patients with GD than in healthy controls [11] or in non-AITD patients [29]. In contrast, Yasuda et al., found that the serum 25(OH) levels of 26 female patients with new-onset GD were lower (35.9 vs. 42.7 nmol/L; \( p < 0.05 \)) and the prevalence of vitamin D deficiency (25(OH)D level < 37.5 nmol/L) was higher (65.4% vs. 32.4%; \( p = 0.05 \)) than that recorded in 46 controls. There was a significant association between serum 25(OH)D levels and thyroid volume \((r = -0.45; p = 0.05)\) [38]. The same research group also reported that serum vitamin D levels were lower in 36 female patients without GD remission compared with 18 patients that had achieved GD remission \((p < 0.005)\) and 49 controls \((p < 0.0005)\) after 1 year [39]. Zhang et al., revealed that serum vitamin D levels in anti-TSHR antibody-positive GD patients were lower than in healthy controls or anti-TSHR antibody-negative patients, and were inversely correlated with anti-TSHR antibody levels, suggesting a possible link between vitamin D status and increased thyroid autoimmunity in GD patients [40].

In addition to the aforementioned meta-analysis, another meta-analysis of 26 studies showed that patients with GD had a higher prevalence of vitamin D deficiency compared to controls with high heterogeneity [44].

Several authors have studied the association between VDR gene polymorphisms (\(\text{ApaI, BsmI, FokI, and TaqI}\)) and AITD risk, although the results are still ambiguous and inconsistent. The first meta-analysis to assess the association between VDR gene polymorphisms and GD comprised seven studies (three Caucasian and four Asian). \(\text{ApaI, BsmI, and FokI}\) polymorphisms in the VDR gene were associated with susceptibility to GD in Asian populations, whereas there was no association between VDR gene polymorphisms and GD in Caucasian populations [45]. In a recent meta-analysis including eight studies (five European, two Asian, and one African), the VDR \(\text{BsmI or TaqI}\) polymorphisms were found to be significantly associated with AITD risk, including HT and GD \((\text{OR 0.801 for B vs. b; OR 0.854 for t vs. T})\), while the \(\text{ApaI and FokI}\) polymorphisms were not. Subgroup analysis of the European studies showed a decreased risk of AITD for the B or t variants [46]. Later, Inoue et al., demonstrated that the frequency of the TT genotype for \(\text{TaqI}\) was higher in GD patients than in HT patients, and the frequency of the C allele for \(\text{ApaI}\) was higher in GD patients than in controls. The frequency of the CC genotype for the \(\text{FokI}\) polymorphism was also higher in HT patients than in control subjects and GD patients. In addition, they reported that the genetic differences in the \(\text{DBP}\) and \(\text{CYP2R1}\) genes might be involved with the intractability of GD [47]. Wang et al., published a meta-analysis of 11 studies (five Caucasian and six Asian) in which the VDR \(\text{FokI}\) polymorphism was found to be associated with HT risk only in the Asian population \((\text{F vs. f; OR = 1.45})\) but not in the Caucasian population. Furthermore, the \(\text{TaqI, ApaI, and BsmI}\) polymorphisms were not positively associated in the overall population, nor when stratified by ethnicity [48].

Pani et al., investigated the association of \(\text{DBP}\)-gene polymorphisms and thyroid autoimmunity in 187 Caucasian families (561 participants). An intron 8 \((\text{TAAA})(n)\) polymorphism was found to be correlated with GD but not with HT [49]. However, a \(\text{CYP27B1}\) intron 6 polymorphism was not associated with GD or HT, as identified by the same authors [50]. In another study analyzing 332 polish patients with GD and 185 healthy controls, the \(\text{DBP}\) gene Lys allele at codon 420 was found to be associated with increased susceptibility to GD [51].

In conclusion, most studies have shown an association between low vitamin D status in the pathogenesis of AITD, especially HT. However, there are only few preliminary interventional studies for HT. Further randomized controlled trials are needed to determine whether there is a causal relationship, and investigate the potential application of vitamin D in the treatment of AITD.
4. Vitamin D and Thyroid Cancers

4.1. Mechanisms

In addition to its main role in calcium homeostasis, vitamin D can directly or indirectly regulate multiple signaling pathways involved in cellular proliferation, differentiation, apoptosis, inflammation, invasion, angiogenesis, and metastasis. Therefore, it has the potential to affect cancer development and growth. Recent findings indicate that vitamin D also regulates microRNA expression and may influence cancer stem cell biology [52].

Both in vitro models and in vivo animal models have demonstrated that vitamin D has anti-proliferative, pro-differentiative, pro-apoptotic, and anti-inflammatory actions within the tumor microenvironment. Perhaps the most recognized anti-neoplastic effect of calcitriol is its ability to inhibit cell proliferation [53]. 1,25(OH)\(_{2}\)D increases the expression of the cyclin-dependent kinase (CDK) inhibitors p21 and p27, and decreases CDK activity, thereby leading to dephosphorylation of the retinoblastoma (Rb) protein and G0/G1 cell cycle arrest. 1,25(OH)\(_{2}\)D has indirect effects on cell cycle regulation through inhibition of mitogenic signaling by growth factors such as insulin-like growth factor 1 (IGF1) and epidermal growth factor (EGF), as well as by inducing increased expression of growth inhibitors such as transforming growth factor-β (TGF-β). In addition, 1,25(OH)\(_{2}\)D modulates intracellular kinase pathways such as p38, MAPK, ERK, and PI3K, represses the proto-oncogene MYC, and inhibits the high telomerase activity characteristic of human cancer cells by decreasing telomerase reverse transcriptase (TERT) mRNA expression [52–54]. Besides its anti-proliferative effects, 1,25(OH)\(_{2}\)D also regulates key mediators of apoptosis such as inhibiting anti-apoptotic proteins (BCL-2 and BCL-X\(_{L}\)) or inducing the expression of pro-apoptotic proteins (BAX, BAK, and BAD). Moreover, 1,25(OH)\(_{2}\)D induces caspase activation [53,54]. 1,25(OH)\(_{2}\)D is a well-known pro-differentiation hormone that regulates the activity of more than 60 genes involved in cell differentiation [53]. Cell type-specific pro-differentiation mechanisms include the regulation of β-catenin, JUN N-terminal kinase, PI3K, and nuclear factor-κB (NF-κB) signaling pathways, as well as regulating the activity of transcription factors such as the activator protein 1 complex and CCAAT/enhancer-binding protein (C/EBP) [52]. 1,25(OH)\(_{2}\)D shows beneficial anti-inflammatory actions in several cancers through key mechanisms including the inhibition of prostaglandin synthesis (by suppressing cyclooxygenase 2 (COX2) expression) and prostaglandin signaling (by upregulating the expression of the catabolic enzyme and repressing the expression of prostaglandin receptors), suppressing p38 stress kinase signaling and subsequent inhibition of the production of pro-inflammatory cytokines, and the inhibition of NF-κB signaling [52,53]. In addition, 1,25(OH)\(_{2}\)D inhibits invasion and metastasis by regulating the expression of components of the plasminogen activator system and matrix metalloproteinases (MMPs) and increasing the expression of E-cadherin, a tumor suppressor gene that is inversely correlated with metastatic potential. 1,25(OH)\(_{2}\)D also inhibits angiogenesis by suppressing the expression of vascular endothelial growth factor (VEGF) [52,53].

Thyroid cancer is the most common endocrine malignancy worldwide, and its incidence is gradually increasing. Risk factors such as exposure to ionizing radiation, chemical genotoxins, and obesity have been implicated in the increasing incidence of thyroid cancer [55]. The molecular pathways involved in thyroid carcinogenesis are becoming increasingly unraveled. Thyroid neoplasia results from genomic instability that is enhanced by risk factors such as exposure to radiation resulting in early genetic alterations (e.g., RET/PTC and PAX8-PPAR\(_{γ}\) rearrangements, BRAF and RAS point mutations) and constitutive activation of thyrocyte signaling pathways. Dedifferentiation is caused by late genetic alterations (e.g., \(p53\) and \(CTNNB1\) mutations), resulting in rapidly expanding and metastatic thyroid cancer [54].

Several preclinical studies have demonstrated growth arrest of thyroid cancer after the administration of pharmacological doses of 1,25(OH)\(_{2}\)D or its analogs in differentiated thyroid cancer (DTC) cell lines. The mechanism underlying the antitumor effect of 1,25(OH)\(_{2}\)D on thyroid cancers were mainly found to result from inhibited proliferation, although the effects of redifferentiation...
and apoptosis were not consistent [54]. Specifically, it has been shown that 1,25(OH)_{2}D inhibits cell proliferation by inhibiting the expression of c-MYC, a well-known proto-oncogene, and stimulates the accumulation of p27, resulting in an increased percentage of cells in the G0-G1 phase of the cell cycle with decreased Ki67 expression. In addition to this, 1,25(OH)_{2}D has also been found to increase cell adhesiveness via increased fibronectin expression, mediated by the PTEN/PI3 kinase pathway [54,55].

4.2. In Vitro and Animal Studies

In vitro, 1,25(OH)_{2}D and a new less-calcemic vitamin D analog, MART-10, could effectively repress ATC cell migration and invasion through reversing cadherin switch, blocking EMT processes, and downregulating the formation of F-actin. As MART-10 shows more potent attenuation of ATC cell metastatic potential than 1,25(OH)_{2}D, and considering that MART-10 has been confirmed to be active in vivo without inducing any obvious side effects, further in vivo study of the applicability of MART-10 for ATC treatment is warranted [56]. In another study, 1,25(OH)_{2}D was shown to inhibit the proliferation of thyroid cancer stem cells derived from ATC via G2/M phase cell cycle arrest [57].

In female SCID mice that were implanted with human thyroid follicular carcinoma-derived (WRO) cells, calcitriol administration was observed to reduce tumor size, enhance cellular differentiation, and prevent metastatic growth as indicated by marked p27 accumulation in the thyroid carcinoma cells [58]. In other study using the same mouse model, treatment with 1,25(OH)_{2}D and its noncalciomimetic analog EB1089 resulted in a 50% reduction in tumor weight through increased cell adhesiveness accompanied by an increase in fibronectin [59].

4.3. Human Studies

Multiple cell culture and animal models of cancer support a role for dietary vitamin D_{3} and calcitriol in impeding cancer development and progression. However, data from human clinical trials are inconsistent [52]. A large number of epidemiological studies have suggested that low circulating levels of 25(OH)D, related to geographical location, diet, and outdoor activity, are associated with a higher risk of cancer incidence and poorer outcomes, although many studies do not demonstrate any associations [52,53]. A recent review of epidemiological evidence of the relationship between vitamin D and colorectal, breast, and prostate cancers reported a consistent inverse association for colorectal cancer incidence and mortality in observational studies, whereas the results for breast cancer have generally shown that higher 25(OH)D levels are associated with a lower risk of progression and mortality [60]. In contrast, the randomized, double-blind clinical trials conducted to date have generally failed to support these findings. For prostate cancer, there is no convincing evidence of an association between 25(OH)D and incidence, progression and mortality, although the results of one open-label clinical trial suggested that supplementation with 4000 IU/day of vitamin D_{3} may inhibit progression of the disease [60].

A few clinical studies have suggested an association between vitamin D status and incidence or worse outcomes of thyroid cancer (Table 2). Roskies et al., retrospectively studied preoperative 25(OH)D levels in 212 patients undergoing thyroidectomy, and showed a higher malignancy rate in the vitamin D-deficient group (25(OH)D level < 37.5 nmol/L) compared to the vitamin D-sufficient group (75% vs. 37.5%), corresponding to a relative risk of 2.0 (p = 0.03), suggesting that vitamin D deficiency is a potentially modifiable risk factor for thyroid cancer [61]. Sahin et al., reported that 344 patients with PTC had significantly lower 25(OH)D levels than 116 controls (42.4 vs. 47.4 nmol/L; p = 0.004), and vitamin D deficiency (25(OH)D level < 50 nmol/L) was more prevalent in this group (166/235 vs. 64/108; p = 0.026). The tumor diameter was also significantly associated with log-vitamin D_{3} concentrations (B = 0.207; p = 0.04) [62]. Kim et al., investigated 548 female patients who underwent total thyroidectomy for PTC. The preoperative 25(OH)D levels were significantly lower in patients with a tumor size of >1 cm (p = 0.041) or lymph node metastasis (p = 0.043). Patients with 25(OH)D levels < 46.2 nmol/L (median) also had a significantly higher risk of T stage 3/4, lymph node metastasis, and progressing to stage III/IV after adjustment [63]. Stepien et al., revealed significantly
lower 1,25(OH)₂D levels in 27 PTC patients, 16 FTC patients, and seven ATC patients compared to 26 healthy controls, and also reported an inverse relationship of lower 1,25(OH)₂D levels with an advanced tumor stage. However, there were no significant differences in 25(OH)D levels [64]. Penna-Martinez et al., showed lower serum 1,25(OH)₂D levels in 172 patients with DTC when compared to 321 healthy controls. While no significant difference in 25(OH)D levels were observed, there was an association between VDR polymorphisms and the incidence of thyroid carcinoma [65]. Later, the same authors investigated vitamin D status and expression of genes related to vitamin D enzymes in 253 patients with DTC and 302 controls, and they showed an association between DTC and low 25(OH)D and 1,25(OH)₂D levels in certain CYP24A1 haplotypes [66].

Besides the aforementioned studies, contrasting data that suggest there is no association between 25(OH)D and thyroid cancer have been reported by other groups. Laney et al., demonstrated that serum 25(OH)D levels and the proportion of patients with 25(OH)D levels <75 nmol/L were not different in 42 cases with thyroid nodules, 45 with thyroid cancer in remission, and 24 active thyroid cancer patients, and these factors were not affected by cancer stage [67]. Jonklaas et al., revealed no associations between preoperative 25(OH)D levels and diagnosis of thyroid cancer, disease stage, or any other prognostic features in 65 euthyroid patients undergoing thyroidectomy for thyroid cancer [68]. Lizis-Kolus et al., demonstrated no difference in serum 25(OH)D levels in 40 female patients with PTC and 40 with HT, and found no relationship between 25(OH)D and the clinical disease stage of patients with PTC [69]. Ahn et al., showed that preoperative 25(OH)D levels were not associated with either disease aggressiveness or poor outcomes among 820 patients with PTC [70]. Danilovic et al., evaluated 433 patients that underwent thyroidectomy for thyroid nodules and observed no significant differences in preoperative 25(OH)D levels or quartile distribution between benign and malignant cases. Decreased 25(OH)D levels were not overtly associated with a poorer prognosis among 187 patients with PTC [71]. The author also investigated 410 patients that underwent ultrasonography-guided fine-needle aspiration for thyroid nodules and found that serum 25(OH)D levels and the prevalence of vitamin D insufficiency (25(OH)D level < 75 nmol/L) did not significantly differ between benign and malignant thyroid nodules. In addition, vitamin D insufficiency was not associated with disease stage or any other prognostic factors among 44 DTC patients [72]. More recently, Choi et al., analyzed 5186 euthyroid subjects with no clinical evidence ofAITD who underwent routine health check-ups, and found that serum 25(OH)D levels were not associated with thyroid cancer prevalence [73].

No convincing associations have been shown for studies that have estimated vitamin D intake and related this to the prevalence of thyroid cancer [55]. In a population-based case-control study, weekly use of a vitamin D supplement was not related to thyroid cancer risk in females from Los Angeles [74]. In contrast, the cross-sectional cohort Vitamins and Lifestyle (VITAL) study showed a positive association between high dietary supplementation of vitamin D and thyroid cancer risk (OR 1.66, 95% CI 1.21–2.28) [75]. The large prospective US National Institutes of Health American Association of Retired Persons (NIH-AARP) Diet and Health Study showed no clear evidence of a positive or negative association between thyroid cancer risk and dietary intake of any micronutrient, including vitamin D [76]. A systematic review suggested that the current evidence to support any protective or hazardous effect of vitamin or mineral supplements, including vitamin D, on thyroid cancer development is inconclusive [77]. Vitamin D levels were not measured in these studies, and inconsistent data may be due to the general poor correlation between vitamin D deficiency and estimates of vitamin D intake [55].
Table 2. Clinical studies for an association between vitamin D status and thyroid cancer.

| Sources                        | Study Subjects                                      | Low Vitamin D Status (25(OH)D Level (nmol/L)) | Criteria | Notable Findings                                                                                                                                 |
|-------------------------------|----------------------------------------------------|-----------------------------------------------|----------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Roskies et al., 2012 [61]     | 212 patients undergoing thyroidectomy              | <37.5 (D)                                     | malignancy rate 75% vs. 37.5% in D and non-D group (RR 2.0, 95% CI 1.07–2.66) (SD)        |
| Sahin et al., 2013 [62]       | 344 PTC, 116 controls                               | <50                                           | 70.6% of PTC, 59.3% of controls; 42.4 vs. 47.4 nmol/L (SD); association between tumor diameter and log-25(OH)D (B = 0.207) (SD) |
| Kim et al., 2014 [63]         | 548 females undergoing total thyroidectomy for PTC | <46.2 (median)                                | higher risk of T stage 3/4, LNM, lateral LNM, stage III/IV (SD); lower 25(OH)D levels in patients with a tumor size >1 cm or LNM (SD) |
| Stepien et al., 2010 [64]     | 50 TC (27 PTC, 16 FTC, 7 ATC), 34 MNG, 26 healthy controls | NA                                            | no difference in 25(OH)D levels; lower 1,25(OH)\textsubscript{2}D levels in TC than controls (SD); inverse relationship between 1,25(OH)\textsubscript{2}D levels and tumor stage (SD) |
| Penna-Martinez et al., 2009   | 172 TC (132 PTC, 40 FTC), 321 healthy controls      | <50                                           | no difference vitamin D deficiency rates and 25(OH)D levels; higher 1,25(OH)\textsubscript{2}D deficiency and lower 1,25(OH)\textsubscript{2}D levels in TC than controls (SD) |
| Penna-Martinez et al., 2012   | 253 TC (205 PTC, 48 FTC), 302 healthy controls      | <25 (DD) 25–50 (D) 50–75 (I) >75 (S)          | no difference in vitamin D status and 25(OH)D levels; lower 1,25(OH)\textsubscript{2}D levels in TC than controls (SD); lower 25(OH)D and 1,25(OH)\textsubscript{2}D levels in TC patients with certain CYP24A1 haplotypes |
| Laney et al., 2010 [67]       | 69 TC (45 in remission, 24 active), 42 benign thyroid nodule patients | <75                                           | no difference vitamin D deficiency rates and 25(OH)D levels |
| Jonkaas et al., 2013 [68]     | 65 euthyroid patients undergoing thyroidectomy      | NA                                            | no association between 25(OH)D levels and malignancy rate, stage, or other prognostic features |
| Lizis-Kolus et al., 2013 [69] | 80 females (40 PTC, 40 HT)                          | NA                                            | no association between 25(OH)D levels and malignancy rate or stage |
| Sources                  | Study Subjects                          | Low Vitamin D Status (25(OH)D Level (nmol/L)) | Notable Findings                                      |
|-------------------------|-----------------------------------------|---------------------------------------------|-------------------------------------------------------|
| Ahn et al., 2016 [70]   | 820 PTC                                 | <24.7                                       | no association between vitamin D status and disease aggressiveness or poor outcomes |
|                         |                                         | 24.7–32.9                                   |                                                       |
|                         |                                         | 33.0–44.1                                   |                                                       |
|                         |                                         | 44.2–110.0                                  |                                                       |
| Danilovic et al., 2016 [71] | 433 patients undergoing thyroidectomy (199 TC, 234 benign nodule) | <50                                         | no difference in vitamin D deficiency rates and 25(OH)D levels |
| Kim, 2016 [72]          | 410 patients undergoing US-guided FNA for thyroid nodules (44 TC, 366 benign) | <75                                         | no difference in vitamin D deficiency and 25(OH)D levels; no association with cancer stage or other prognostic features |
| Choi et al., 2017 [73]  | 5186 euthyroid subjects without AITD undergoing routine health check-ups (53 TC) | <25 (D)                                     | no difference in vitamin D status and 25(OH)D levels |
|                         |                                         | 25–75 (I)                                   |                                                       |
|                         |                                         | 75–125 (S)                                  |                                                       |
|                         |                                         | >125 (E)                                    |                                                       |

25(OH)D, 25-hydroxyvitamin D; D, deficient; RR, relative risk; SD, significant difference; CI, confidence interval; PTC, papillary thyroid cancer; LNM, lymph node metastasis; TC, thyroid cancer; FTC, follicular thyroid cancer; ATC, anaplastic thyroid cancer; MNG, multinodular nontoxic goiter; NA, not available; 1,25(OH)\textsubscript{2}D, 1,25-dihydroxyvitamin D; DD, severely deficient; I, insufficient; S, sufficient; CYP24A1, 24-hydroxylase; HT, Hashimoto’s thyroiditis; US, ultrasonography; FNA, fine-needle aspiration; AITD, autoimmune thyroid disease; E, excess.
The VDR is expressed in both normal and malignant thyroid tissue [54]. Moreover, VDR and CYP27B1 expressions were found to be increased in papillary thyroid cancer (PTC) when compared to normal thyroid tissue [78]. Later, these findings were reproduced by other groups which reported that VDR, CYP27B1, and CYP24A1 expressions were increased in follicular adenoma and DTC, such as PTC and follicular thyroid cancer (FTC), when compared to normal thyroid tissue [79]. When DTC was compared to follicular adenoma, significantly higher VDR and lower CYP24A1 expression was observed. The high VDR/low CYP24A1 profile in DTC might suggest a stronger antitumor response, increasing the local availability and reactivity of 1,25(OH)2D [54,79]. However, in PTC with lymph node metastasis, VDR and CYP24A1 were decreased compared with non-metastasized PTC, along with decreased expression of CDK inhibitors [79]. In anaplastic thyroid cancer (ATC), VDR expression is often lost. Moreover, ATC with high Ki67 expression or distant metastases at diagnosis was characterized by more negative VDR/CYP24A1/CYP27B1 staining [79]. In conclusion, increased expression of key players involved in local 1,25(OH)2D signaling was demonstrated in benign and differentiated malignant thyroid tumors, but a decrease or complete loss of expression was observed for local nodal and especially distant metastasis of ATC, suggesting a local antitumor response of 1,25(OH)2D in the early stages of cancer [79]. In addition, the mRNA expression of VDR and genes regulating cell–cell and cell–matrix adhesion and degradation of the extracellular matrix (ECM), ECM1 and type II transmembrane serine protease-4 (TMPRSS4) were higher in PTC samples compared to normal thyroid tissue from the same patients. Increased VDR expression was often linked to increased expression of ECM1 and/or TMPRSS4, both of which are potential markers of PTC. ECM1 promotes blood vessel formation, stimulating the proliferation of malignant epithelial cells and leading to tumor progression, and TMPRSS4 modulates invasion, metastasis, migration, and adhesion, as well as epithelial–mesenchymal transition (EMT) in cancer cells. Up-regulation of ECM1 or TMPRSS4 has been reported in numerous malignant epithelial tumors, and is an independent predictor of a thyroid carcinoma [80]. In addition to being elevated in PTC, VDR mRNA overexpression was recently reported to be correlated with worse prognostic factors, such as subtypes of PTC with a poorer prognosis, lateral neck node metastasis, advanced stage, and recurrence-free survival [81].

Significant associations with VDR polymorphisms have been reported for prostate (Fok1, Bsm1, and Taq1), breast (Fok1, Bsm1, and Apa1), colon-rectum (Fok1, Bsm1, and Taq1), and skin (Fok1, Bsm1, and Taq1) cancers [82]. However, only two studies have investigated the association between VDR polymorphisms and thyroid cancer risk. One showed no difference in VDR polymorphisms between 71 DTC patients and 82 healthy controls [83]. The other revealed that while the AA and FF alleles of the Apal and Fok1 VDR polymorphisms and the tABF haplotype confer protection against FTC, the Tabf haplotype appeared to be associated with an increased FTC risk in 172 DTC patients and 321 healthy controls [65].

In summary, although many preclinical studies suggest an association between vitamin D and thyroid cancer, only a few conflicting case-control studies have been reported. To date, no interventional, randomized controlled trials have been published, and further studies are needed.

5. Limitations in the Study of Vitamin D

Although many studies have suggested an association of low vitamin D status with AITD and thyroid cancer, epidemiological studies simply show correlative relationships which cannot be used to determine cause and effect [3,72]. Low vitamin D status may be not the cause but rather a consequence of the disease [41,84]. The low vitamin D levels of patients with thyroid diseases can be explained by low vitamin D intake, malabsorption, lack of sun exposure, or reduced outdoor activity [21,29,72,84,85]. In addition, it is likely that good vitamin D status represents a general marker of good health. A young individual with a normal body weight and a healthy lifestyle, including good dietary and exercise habits, is more likely to have higher 25(OH)D levels, but also a lower risk of cancer or chronic illness. Therefore, it is difficult to separate the effects of these characteristics from those that may be attributed to 25(OH)D levels [55,76,86]. Similarly, low vitamin D status may be the result of
chronic illness, which prevents outdoor activities and sun exposure. Vitamin D is rarely ingested in isolation; therefore, additional nutrients that are co-ingested with vitamin D may have independent or synergistic effects [86]. Additionally, because serum vitamin D levels were measured only once in almost all observational studies, the values obtained might not be representative [70,72,86].

The controversial and varying results of studies are partly due to inter-assay and inter-laboratory variability in the measurements of 25(OH)D, seasonal variations in blood sampling of 25(OH)D, and the different cut-off levels used to define vitamin D deficiency or insufficiency. In addition, the conflicting results could be explained by limitations in study design, such as cross-sectional studies with a small number of subjects, and therefore, the potential for selection bias, as well as the heterogeneity of the study population and the diverse methods used for the diagnosis of AITD, HT, GD, or thyroid cancer [11,29,41,72]

6. Conclusions

The pleiotropic roles of vitamin D have been recognized through preclinical and observational studies which have suggested a beneficial role of vitamin D in the management of thyroid disease. However, only an ambiguous causal relationship and few interventional studies have been reported to date, so the preventive and therapeutic potential of vitamin D or its analog in thyroid diseases remains debated. Ongoing and future long-term, randomized controlled trials are required to determine whether individuals with low 25(OH)D levels are at increased risk of developing AITD and thyroid cancer, and to provide insight into the efficacy and safety of vitamin D as a therapeutic tool for these thyroid diseases.

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References
1. Makariou, S.; Liberopoulos, E.N.; Elisaf, M.; Challa, A. Novel roles of vitamin D in disease: What is new in 2011? *Eur. J. Intern. Med.* 2011, 22, 355–362. [CrossRef] [PubMed]
2. Holick, M.F. Vitamin D deficiency. *N. Engl. J. Med.* 2007, 357, 266–281. [CrossRef] [PubMed]
3. Plum, L.A.; DeLuca, H.F. Vitamin D, disease and therapeutic opportunities. *Nat. Rev. Drug Discov.* 2010, 9, 941–955. [CrossRef] [PubMed]
4. Muscogiuri, G.; Tirabassi, G.; Bizzaro, G.; Orto, F.; Paschou, S.A.; Vryonidou, A.; Balercia, G.; Shoenfeld, Y.; Colao, A. Vitamin D and thyroid disease: To D or not to D? *Eur. J. Clin. Nutr.* 2015, 69, 291–296. [CrossRef] [PubMed]
5. Kmiec, P.; Sworczak, K. Vitamin D in thyroid disorders. *Exp. Clin. Endocrinol. Diabetes* 2015, 123, 386–393. [CrossRef] [PubMed]
6. Vondra, K.; Stárka, L.; Hampl, R. Vitamin D and thyroid diseases. *Physiol. Res.* 2015, 64, S95–S100. [PubMed]
7. Bikle, D. Nonclassic actions of vitamin D. *J. Clin. Endocrinol. Metab.* 2009, 94, 26–34. [CrossRef] [PubMed]
8. Prietl, B.; Treiber, G.; Pieber, T.R.; Amrein, K. Vitamin D and immune function. *Nutrients* 2013, 5, 2502–2521. [CrossRef] [PubMed]
9. Wacker, M.; Holick, M.F. Vitamin D—Effects on skeletal and extraskeletal health and the need for supplementation. *Nutrients* 2013, 5, 111–148. [CrossRef] [PubMed]
10. Holick, M.F.; Binkley, N.C.; Bischoff-Ferrari, H.A.; Gordon, C.M.; Hanley, D.A.; Heaney, R.P.; Murad, M.H.; Weaver, C.M. Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 2011, 96, 1911–1930. [CrossRef] [PubMed]
11. D’Aurizio, F.; Villalta, D.; Metus, P.; Doretto, P.; Tozzoli, R. Is vitamin D a player or not in the pathophysiology of autoimmune thyroid diseases? *Autoimmun. Rev.* 2015, 14, 363–369. [CrossRef] [PubMed]
12. Klecha, A.J.; Barreiro Arcos, M.L.; Frick, L.; Genaro, A.M.; Cremaschi, G. Immune-endocrine interactions in autoimmune thyroid diseases. *Neuroimmunomodulation* 2008, 15, 68–75. [CrossRef] [PubMed]
13. Fountoulakis, S.; Tatsoulis, A. On the pathogenesis of autoimmune thyroid disease: A unifying hypothesis. *Clin. Endocrinol.* 2004, 60, 397–409. [CrossRef] [PubMed]
14. Baeke, F.; Takiishi, T.; Korf, H.; Gyselms, C.; Mathieu, C. Vitamin D: Modulator of the immune system. *Curr. Opin. Pharmacol.* 2010, 10, 482–496. [CrossRef] [PubMed]

15. Mathieu, C.; Adorini, L. The coming of age of 1,25-dihydroxyvitamin D3 analogs as immunomodulatory agents. *Trends Mol. Med.* 2002, 8, 174–179. [CrossRef]

16. Hewison, M. An update on vitamin D and human immunity. *Clin. Endocrinol.* 2012, 76, 315–325. [CrossRef] [PubMed]

17. Fournier, C.; Gepner, P.; Sadouk, M.; Charriere, J. In vivo beneficial effects of cyclosporin A and 1,25-dihydroxyvitamin D3 on the induction of experimental autoimmune thyroiditis. *Clin. Immunol. Immunopathol.* 1990, 54, 53–63. [CrossRef]

18. Chen, W.; Lin, H.; Wang, M. Immune intervention effects on the induction of experimental autoimmune thyroiditis. *J. Huazhong Univ. Sci. Technol. Med. Sci.* 2002, 22, 343–345. [CrossRef] [PubMed]

19. Liu, S.; Xiong, F.; Liu, E.M.; Zhu, M.; Lei, P.Y. Effects of 1,25-dihydroxyvitamin D3 in rats with experimental autoimmune thyroiditis. *J. Endocrinol. Invest.* 2010, 33, 1573–1576.

20. Misharin, A.; Hewison, M.; Chen, C.R.; Lagishetty, V.; McLaughlan, S.M. Vitamin D deficiency modulates Graves’ hyperthyroidism induced in BALB/c mice by thyrotropin receptor immunization. *Endocrinology* 2009, 50, 1051–1060. [CrossRef] [PubMed]

21. Kivity, S.; Agmon-Levin, N.; Zisappl, M.; Shapira, Y.; Nagy, E.V.; Dankô, K.; Szekanecz, Z.; Langevitz, P.; Shoenfeld, Y. Vitamin D and autoimmune thyroid diseases. *Cell. Mol. Immunol.* 2011, 8, 243–247. [CrossRef] [PubMed]

22. Tamer, G.; Arik, S.; Tamer, I.; Coksert, D. Relative vitamin D insufficiency in Hashimoto’s thyroiditis. *Thyroid* 2011, 21, 891–896. [CrossRef] [PubMed]

23. Bozkurt, N.C.; Karbek, B.; Ucan, B.; Sahin, M.; Cakal, E.; Ozbek, M.; Delibasi, T. The association between severity of vitamin D deficiency and Hashimoto’s thyroiditis. *Endocr. Pract.* 2013, 19, 479–484. [CrossRef] [PubMed]

24. Mansournia, N.; Mansournia, M.A.; Saeedi, S.; Dehghan, J. The association between serum 25OHD levels and hypothyroid Hashimoto’s thyroiditis. *J. Endocrinol. Investig.* 2014, 37, 473–476. [CrossRef] [PubMed]

25. Shin, D.Y.; Kim, K.J.; Kim, D.; Hwang, S.; Lee, E.J. Low serum vitamin D is associated with anti-thyroid peroxidase antibody in autoimmune thyroiditis. *Yonsei Med. J.* 2014, 55, 476–481. [CrossRef] [PubMed]

26. Unal, A.D.; Tarcin, O.; Parildar, H.; Cigerli, O.; Eroglu, H.; Demirag, N.G. Vitamin D deficiency is related to thyroid antibodies in autoimmune thyroiditis. *Cent. Eur. J. Immunol.* 2014, 39, 493–497. [CrossRef] [PubMed]

27. Choi, Y.M.; Kim, W.G.; Kim, T.Y.; Bae, S.J.; Kim, H.K.; Jang, E.K.; Jeon, M.J.; Han, J.M.; Lee, S.H.; Baek, J.H.; et al. Low levels of serum vitamin D3 are associated with autoimmune thyroid disease in pre-menopausal women. *Thyroid* 2014, 24, 655–661. [CrossRef] [PubMed]

28. Wang, X.; Zynat, J.; Guo, Y.; Osiman, R.; Tuhuti, A.; Zhao, H.; Abdunaimu, M.; Wang, H.; Jin, X.; Xing, S. Low serum vitamin D is associated with anti-thyroid-globulin antibody in female individuals. *Int. J. Endocrinol.* 2015, 2015, 285290. [CrossRef] [PubMed]

29. Kim, D. Low vitamin D status is associated with hypothyroid Hashimoto’s thyroiditis. *Hormones* 2016, 15, 385–393. [CrossRef] [PubMed]

30. Wang, J.; Lv, S.; Chen, G.; Gao, C.; He, J.; Zhong, H.; Xu, Y. Meta-analysis of the association between vitamin D and autoimmune thyroid disease. *Nutrients* 2015, 7, 2485–2498. [CrossRef] [PubMed]

31. Muscogiuri, G.; Mari, D.; Prolo, S.; Fatti, L.M.; Cantone, M.C.; Garagnani, P.; Arosio, B.; Di Somma, C.; Vitale, G. 25 Hydroxyvitamin D deficiency and its relationship to autoimmune thyroid disease in the elderly. *Int. J. Environ. Res. Public Health* 2016, 13, E850. [CrossRef] [PubMed]

32. Camurdan, OM.; Döger, E.; Bideci, A.; Celik, N.; Cinaz, P. Vitamin D status in children with Hashimoto thyroiditis. *J. Pediatr. Endocrinol. Metab.* 2012, 25, 467–470. [CrossRef] [PubMed]

33. Evişiyaoğlu, O.; Acar, M.; Özcabı, B.; Erginöz, E.; Bucak, F.; Ercan, O.; Kucur, M. Vitamin D deficiency and Hashimoto’s thyroiditis in children and adolescents: A critical vitamin D level for this association? *J. Clin. Res. Pediatr. Endocrinol.* 2015, 7, 128–133. [CrossRef] [PubMed]

34. Metwalley, K.A.; Farghaly, H.S.; Sherief, T.; Hussein, A. Vitamin D status in children and adolescents with autoimmune thyroiditis. *J. Endocrinol. Invest.* 2016, 39, 793–797. [CrossRef] [PubMed]

35. Goswami, R.; Marwaha, R.K.; Gupta, N.; Tandon, N.; Sreenivas, V.; Tomar, N.; Ray, D.; Kanwar, R.; Agarwal, R. Prevalence of vitamin D deficiency and its relationship with thyroid autoimmunity in Asian Indians: A community-based survey. *Br. J. Nutr.* 2009, 102, 382–386. [CrossRef] [PubMed]
36. Effraimidis, G.; Badenhoop, K.; Tijssen, J.G.; Wiersinga, W.M. Vitamin D deficiency is not associated with early stages of thyroid autoimmunity. *Eur. J. Endocrinol.* 2012, 167, 43–48. [CrossRef] [PubMed]

37. Mazokopakis, E.E.; Papadomanolaki, M.G.; Tsekouras, K.C.; Evangelopoulos, A.D.; Kotsiris, D.A.; Tzortzinis, A.A. Is vitamin D related to pathogenesis and treatment of Hashimoto’s thyroiditis? *Heli. J. Nucl. Med.* 2015, 18, 222–227. [PubMed]

38. Chaudhary, S.; Dutta, D.; Kumar, M.; Saha, S.; Mondal, S.A.; Kumar, A.; Mukhopadhyay, S. Vitamin D supplementation reduces thyroid peroxidase antibody levels in patients with autoimmune thyroid disease: An open-labeled randomized controlled trial. *Indian J. Endocrinol. Metab.* 2016, 20, 391–398. [CrossRef] [PubMed]

39. Inoue, N.; Watanabe, M.; Ishido, N.; Katsumata, Y.; Kagawa, T.; Hidaka, Y.; Iwatani, Y. The functional polymorphisms of VDR, GC and CYP2R1 are involved in the pathogenesis of autoimmune thyroid diseases. *Clin. Exp. Immunol.* 2014, 178, 262–269. [CrossRef] [PubMed]

40. Pani, M.A.; Regulla, K.; Segni, M.; Hofmann, S.; Hüfner, M.; Pasquino, A.M.; Usadel, K.H.; Badenhoop, K. A polymorphism within the vitamin D-binding protein gene is associated with Graves’ disease but not with Hashimoto’s thyroiditis. *J. Clin. Endocrinol. Metab.* 2002, 87, 2564–2567. [PubMed]

41. Pani, M.A.; Regulla, K.; Segni, M.; Krause, M.; Hofmann, S.; Hüfner, M.; Herwig, J.; Pasquino, A.M.; Usadel, K.H.; Badenhoop, K. Vitamin D 1alpha-hydroxylase (CYP1alpha) polymorphism in Graves’ disease, Hashimoto’s thyroiditis. *Exp. Clin. Endocrinol. Diabetes* 2012, 167, 43–48. [CrossRef] [PubMed]

42. M. D. K.; Bednarczuk, T.; Badenhoop, K. Vitamin D-binding protein (DBP) gene polymorphism is associated with Graves’ disease and the vitamin D status in a Polish population study. *Exp. Clin. Endocrinol. Diabetes* 2006, 114, 329–335. [CrossRef] [PubMed]

43. Feldman, D.; Krishnan, A.V.; Swami, S.; Giovannucci, E.; Feldman, B.J. The role of vitamin D in reducing cancer risk and progression. *Nat. Rev. Cancer* 2014, 14, 342–357. [CrossRef] [PubMed]

44. Diaz, L.; Diaz-Muñoz, M.; Garcia-Gaytán, A.C.; Méndez, I. Mechanistic effects of calcitriol in cancer biology. *Nutrients* 2015, 7, 4154. [PubMed]

45. Clinckspoor, I.; Verlinden, L.; Mathieu, C.; Bouillon, R.; Verslyt, A.; Decallonne, B. Vitamin D in thyroid tumorigenesis and development. *Prog. Histochem. Cytochem.* 2013, 48, 65–98. [CrossRef] [PubMed]

46. Morand, G.B.; da Silva, S.D.; Hier, M.P.; Alaloui-Jamali, M.A. Insights into genetic and epigenetic determinants with impact on vitamin D signaling and cancer association studies: The case of thyroid cancer. *Front. Oncol.* 2014, 4, 309. [CrossRef] [PubMed]
56. Chiang, K.C.; Kuo, S.F.; Chen, C.H.; Ng, S.; Lin, S.F.; Yeh, C.N.; Chen, L.W.; Takano, M.; Chen, T.C.; Juang, H.H.; et al. MART-10, the vitamin D analog, is a potent drug to inhibit anaplastic thyroid cancer cell metastatic potential. Cancer Lett. 2015, 369, 76–85. [CrossRef] [PubMed]

57. Peng, W.; Wang, K.; Zheng, R.; Derwahl, M. 1,25 dihydroxyvitamin D3 inhibits the proliferation of thyroid cancer stem-like cells via cell cycle arrest. Endocr. Res. 2016, 41, 71–80. [CrossRef] [PubMed]

58. Dackiw, A.P.; Ezzat, S.; Huang, P.; Liu, W.; Asa, S.L. Vitamin D3 administration induces nuclear p27 accumulation, restores differentiation, and reduces tumor burden in a mouse model of metastatic follicular thyroid cancer. Endocrinology 2004, 145, 5840–5846. [CrossRef] [PubMed]

59. Liu, W.; Asa, S.L.; Ezzat, S. 1α,25-Dihydroxyvitamin D3 targets PTEN-dependent fibronectin expression in thyroid cancer. J. Endocrinol. Metab. 2009, 84, 660–666. [CrossRef] [PubMed]

60. Jacobs, E.T.; Kohler, L.N.; Kunihiro, A.G.; Jurutka, P.W. Vitamin D and colorectal, breast, and prostate cancers: A review of the epidemiological evidence. J. Cancer 2016, 7, 232–240. [CrossRef] [PubMed]

61. Roskies, M.; Dolev, Y.; Caglar, D.; Hier, M.P.; Mlynarek, A.; Majdan, A.; Payne, R.J. Vitamin D deficiency as a potentially modifiable risk factor for thyroid cancer. J. Otolaryngol. Head Neck Surg. 2012, 41, 160–163. [PubMed]

62. Sahin, M.; Uçan, B.; Giniş, Z.; Topaloğlu, O.; Güngüneş, A.; Bozkurt, N.C.; Arslan, M.S.; Ünsal, İ.O.; Akkaymak, E.T.; Demirci, T.; et al. Vitamin D3 levels and insulin resistance in papillary thyroid cancer patients. Med. Oncol. 2013, 30, 589. [CrossRef] [PubMed]

63. Kim, J.R.; Kim, B.H.; Kim, S.M.; Oh, M.Y.; Kim, W.J.; Jeon, Y.K.; Kim, S.S.; Lee, B.J.; Kim, Y.K.; Kim, I.J. Low serum 25 hydroxyvitamin D is associated with poor clinicopathologic characteristics in female patients with papillary thyroid cancer. Thyroid 2014, 24, 1618–1624. [CrossRef] [PubMed]

64. Stepien, T.; Krupinski, R.; Sopinski, J.; Kuzdak, K.; Komorowski, J.; Lawnicka, H.; Stepień, H. Decreased 1-25 dihydroxyvitamin D3 concentration in peripheral blood serum of patients with thyroid cancer. Arch. Med. Res. 2010, 41, 190–194. [CrossRef] [PubMed]

65. Penna-Martinez, M.; Ramos-Lopez, E.; Stern, J.; Hinsch, N.; Hansmann, M.L.; Selkinski, I.; Grünwald, F.; Vorländer, C.; Wahl, R.A.; Bechstein, W.O.; et al. Vitamin D receptor polymorphisms in differentiated thyroid carcinoma. Thyroid 2009, 19, 623–628. [CrossRef] [PubMed]

66. Penna-Martinez, M.; Ramos-Lopez, E.; Stern, J.; Kahles, H.; Hinsch, N.; Hansmann, M.L.; Selkinski, I.; Grünwald, F.; Vorländer, C.; Bechstein, W.O.; et al. Impaired vitamin D activation and association with CYP24A1 haplotypes in differentiated thyroid carcinoma. Thyroid 2012, 22, 709–716. [CrossRef] [PubMed]

67. Laney, N.; Meza, J.; Lyden, E.; Erickson, J.; Treude, K.; Goldner, W. The prevalence of Vitamin D deficiency is similar between thyroid nodule and thyroid cancer patients. Int. J. Endocrinol. 2010, 2010, 805716. [CrossRef] [PubMed]

68. Jonklaas, J.; Danilenos, M.; Wang, H. A pilot study of serum selenium, vitamin D, and thyrotropin concentrations in patients with thyroid cancer. Thyroid 2013, 23, 1079–1086. [CrossRef] [PubMed]

69. Lizio-Kolus, K.; Hubalewska-Dydejczyk, A.; Trofimniuk-Mulder, M.; Sowa-Staszcza, A.; Kowalska, A. Assessment of 25(OH)D3, concentration levels in patients with papillary thyroid cancer compared to patients with Hashimoto’s thyroiditis. Prz. Lek. 2013, 70, 920–925. [PubMed]

70. Ayn, H.Y.; Chung, Y.J.; Park, K.Y.; Cho, B.Y. Serum 25-Hydroxyvitamin D level does not affect the aggressiveness and prognosis of papillary thyroid cancer. Thyroid 2016, 26, 429–433. [CrossRef] [PubMed]

71. Danilovic, D.L.; Ferraz-de-Souza, B.; Fabri, A.W.; Santana, N.O.; Kulesar, M.A.; Cernea, C.R.; Marui, S.; Hoff, A.O. 25-Hydroxyvitamin D and TSH as risk factors or prognostic markers in thyroid carcinoma. PLoS ONE 2016, 11, e0164350. [CrossRef] [PubMed]

72. Kim, D. Low vitamin D status is not associated with thyroid cancer risk. J. Endocrinol. Metab. 2016, 6, 116–122. [CrossRef]

73. Choi, Y.M.; Kim, W.G.; Kim, T.Y.; Bae, S.J.; Kim, H.K.; Jang, E.K.; Jeon, M.J.; Han, J.M.; Shong, Y.K.; Kim, W.B. Serum vitamin D3 levels are not associated with thyroid cancer prevalence in euthyroid subjects without autoimmune thyroid disease. Korean J. Intern. Med. 2017, 32, 102–108. [CrossRef] [PubMed]

74. Mack, W.J.; Preston-Martin, S.; Bernstein, L.; Qian, D. Lifestyle and other risk factors for thyroid cancer in Los Angeles County females. Ann. Epidemiol. 2002, 12, 395–401. [CrossRef]

75. Greenlee, H.; White, E.; Patterson, R.E.; Kristal, A.R. Supplement use among cancer survivors in the Vitamins and Lifestyle (VITAL) study cohort. J. Altern. Complement. Med. 2004, 10, 660–666. [CrossRef] [PubMed]
76. O’Grady, T.J.; Kitahara, C.M.; DiRienzo, A.G.; Gates, M.A. The association between selenium and other micronutrients and thyroid cancer incidence in the NIH-AARP Diet and Health Study. *PLoS ONE* 2014, 9, e110886. [CrossRef] [PubMed]

77. Zhang, L.R.; Sawka, A.M.; Adams, L.; Hatfield, N.; Hung, R.J. Vitamin and mineral supplements and thyroid cancer: A systematic review. *Eur. J. Cancer Prev.* 2013, 22, 158–168. [CrossRef] [PubMed]

78. Khadzkou, K.; Buchwald, P.; Westin, G.; Dralle, H.; Akerström, G.; Hellman, P. 25-hydroxyvitamin D3 1alpha-hydroxylase and vitamin D receptor expression in papillary thyroid carcinoma. *J. Histochem. Cytochem.* 2006, 54, 355–361. [CrossRef] [PubMed]

79. Clinckspoor, I.; Hauben, E.; Verlinden, L.; Van den Bruel, A.; Vanwalleghem, L.; Vander Poorten, V.; Delaere, P.; Mathieu, C.; Verstuyf, A.; Decallonne, B. Altered expression of key players in vitamin D metabolism and signaling in malignant and benign thyroid tumors. *J. Histochem. Cytochem.* 2012, 60, 502–511. [CrossRef] [PubMed]

80. Izkhakov, E.; Somjen, D.; Sharon, O.; Knoll, E.; Aizic, A.; Fliss, D.M.; Limor, R.; Stern, N. Vitamin D receptor expression is linked to potential markers of human thyroid papillary carcinoma. *J. Steroid Biochem. Mol. Biol.* 2016, 159, 26–30. [CrossRef] [PubMed]

81. Choi, J.Y.; Yi, J.W.; Lee, J.H.; Song, R.Y.; Yu, H.; Kwon, H.; Chai, Y.J.; Kim, S.J.; Lee, K.E. VDR mRNA overexpression is associated with worse prognostic factors in papillary thyroid carcinoma. *Endocr. Connect.* 2017, 6, 172–178. [CrossRef] [PubMed]

82. Gandini, S.; Gnagnarella, P.; Serrano, D.; Pasquali, E.; Raimondi, S. Vitamin D receptor polymorphisms and cancer. *Adv. Exp. Med. Biol.* 2014, 810, 69–105. [PubMed]

83. Haghpanah, V.; Ghaffari, S.H.; Rahimpour, P.; Abbasi, A.; Saeedi, M.; Pak, H.; Alborzi, F.; Barzegar, S.; Heshmat, R.; Alimoghadam, K.; et al. Vitamin D receptor gene polymorphisms in patients with thyroid cancer. *Gene Ther. Mol. Biol.* 2007, 11, 299–304.

84. Muscogiuri, G.; Mitri, J.; Mathieu, C.; Badenhoop, K.; Tamer, G.; Orio, F.; Mezza, T.; Vieth, R.; Colao, A.; Pittas, A. Mechanisms in endocrinology: Vitamin D as a potential contributor in endocrine health and disease. *Eur. J. Endocrinol.* 2014, 171, R101–R110. [CrossRef] [PubMed]