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Vitamin D and Autoimmune Thyroiditis: A Systematic Review to Establish a Clinical Immunological Relationship

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Abstract:

Autoimmune thyroiditis is a class of thyroid gland illnesses defined by aberrant lymphocyte activity directed against self-tissues. It is mainly represented by HT and GD, affecting roughly 2% to 3% of the population with a female predominance. The cause of autoimmune thyroiditis is uncertain. However, along with genetic and epigenetic variables, various environmental factors increase AIT risk. Beyond its role in bone health, the widespread expression of vitamin D receptors has demonstrated benefits across many systems. To gain a better understanding of the effects of serum 25(OH)D on thyroid disease, we sought to compile and summarise the literature on vitamin D's impact on AITD by searching electronic databases (PubMed, Google Scholar, and CrossRef) from September to December 2024. The abundance of evidence supported the findings, which suggested that a deficiency in vitamin D is significantly associated with an increased risk of autoimmune thyroiditis, as well as an inverse association between serum 25(OH)D concentration and anti-thyroid antibody titers. Knowing risk factors helps one modify their diet and lifestyle to lower the risk of developing the disease and to slow the progression of autoimmune thyroiditis.

Keywords: Autoimmune thyroiditis, Hypothyroidism, Graves'disease, Vitamin D

1-Introduction

Recently, the prevalence of thyroid disorders, both hypothyroidism and hyperthyroidism, has risen significantly, becoming a global concern. In addition to its effects on individuals' psychological health and quality of life, thyroid disorders also impact human health and vital bodily functions. They are associated with changes in mood, weight, energy, metabolism, heart function, and the nervous system, directly impacting the quality of life of those affected. Therefore, this article has reviewed the existing literature on thyroid problems and the most important risk factors

associated with them, such as the effect of vitamin D deficiency. Due to conflicting results from some studies on the relationship between vitamin D deficiency and thyroid disorders, we designed this study to provide an in-depth review of current knowledge regarding vitamin D's impact on autoimmune thyroid disease, its potential contribution to disease progression, and strategies for management.

1. Thyroid disorder: Thyroiditis

Thyroiditis refers to inflammation of the thyroid gland, which may be associated with thyroid dysfunction. This condition is classified according to the type of clinical manifestations (symptomatic or asymptomatic), the temporal evolution of the disorder (acute, sub-acute, or chronic), and the underlying etiological factors (including autoimmune mechanisms, infectious agents, pharmacological treatments, or radiation exposure) [1]. Indeed, thyroiditis can cause both temporary and permanent thyroid malfunction, including hypothyroidism and hyperthyroidism. The disorder can affect thyroid hormone levels, leading to either a drop (hypothyroidism) or an increase (hyperthyroidism) in production and release, which may be transient or persistent based on the underlying pathology and its treatment [2].

1.1 Hypothyroidism

One common endocrine disorder marked by reduced thyroid hormone synthesis is hypothyroidism. Biochemically, it is characterised by decreased blood T3 and T4 levels, leading to an elevated serum thyroid-stimulating hormone (TSH) concentration. It is a common disease with varying prevalence throughout different nations [3]. Iodine deficiency is the predominant cause worldwide in underdeveloped regions. The prolonged adaptation to an iodine-deficient diet may contribute to hypothyroidism, alongside several environmental factors such as deficiencies in vitamin D and selenium [2]. Hypothyroidism can be categorized based on the site of malfunction as [4]:

- primary (thyroid gland dysfunction)
- secondary (pituitary dysfunction)
- tertiary (hypothalamic dysfunction)

Women have 8–9 times more primary hypothyroidism than males, and incidence rises with age, peaking between 30 and 50. Dry skin, cold intolerance, fatigue, muscle cramps, voice changes, constipation, menorrhagia, and weight gain are common hypothyroidism symptoms, but they vary by age, sex, and the interval between onset and diagnosis [5].

1.2 Hyperthyroidism

An overabundance of thyroid hormones in tissues is called hyperthyroidism, which leads to a distinct clinical condition [5]. The prevalence of hyperthyroidism was calculated at 0.2% for men and 2% for women. The most

common signs of hyperthyroidism include weight loss, weariness, heat sensitivity, warm skin, hair loss, osteoporosis, weakness, and an increased risk of fractures, which are also prevalent in musculoskeletal problems [6, 7].

1.3 Autoimmune Thyroid Disorder

Although data from various regions and countries differ in reporting the prevalence of the most common thyroid diseases, thyroid autoimmunity is the predominant cause of thyroid disorders; nonetheless, Graves' and Hashimoto's diseases are regarded as the most prevalent forms [7].

1.3.1 Graves' Disease

Graves' disease is the predominant etiology of hyperthyroidism in the United States. It is an autoimmune disorder wherein thyroid-stimulating antibodies induce thyroid hormone synthesis by activating TSH receptors. Female gender and a personal or familial history of autoimmune disease are also risk factors for Graves' disease [8, 9].

Graves' disease (GD) is thought to be the most common autoimmune disease, affecting 10 times more women than men. Genes in the major histocompatibility complex and the cytotoxic T-lymphocyte-associated antigen can make an individual more likely to develop Graves' disease. Additionally, non-genetic factors like smoking, pregnancy, estrogen-containing medications, and stressful life events can result in hyperthyroidism [10]. Autoantibodies targeting the thyroid-stimulating hormone receptor (TR-Ab) caused the thyroid gland to produce excess thyroid hormone and enlarge. Autoantibodies against thyroid peroxidase (TPO-Ab) play a significant role in the death of thyrocytes and the onset of autoimmunity. TR-Abs bind to and activate TSH receptors in Graves' disease, thereby increasing follicular hypertrophy, hyperplasia, thyroid hormone production, and the T3-to-T4 ratio. Thyrocytes that express HLA-R molecules can act as antigen-presenting cells (APCs) and activate local T cells by producing co-stimulatory molecules. Cytokines are chemicals that make thyroid-specific T lymphocytes and B cells function, which leads to TR-Ab [11].

1.3.2 Hashimoto's thyroiditis

Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis, is the most prevalent organ-specific autoimmune disease and the primary cause of thyroid hypofunction, with a frequency of 0.3–1.5 cases per 1000 individuals in developed nations [12, 13]. The combined effects of genetic factors (approximately 70%), environmental variables (20–30%), and existential factors are thought to be responsible for HT [14]. The primary hallmarks of Hashimoto's thyroiditis include lymphocytic infiltration of the thyroid gland, leading to gradual tissue destruction and the production of thyroid autoantibodies, specifically thyroglobulin antibodies (Tg-Ab) and thyroid peroxidase antibodies (TPO-Ab). Anti-thyroid antibodies and ultrasonography are distinctive features and valuable indicators for diagnosing this condition. Laboratory analyses indicate that more than 90% of Hashimoto's cases and 40%-70% of Graves’ cases have autoantibodies, regardless of thyroid functional status [15, 16]. As the autoimmune

process progressively diminishes thyroid function, a compensatory phase ensues in which normal thyroid hormone levels are maintained by increased thyroid-stimulating hormone. Subsequently, TSH levels increase further, and symptoms appear, indicating clinical hypothyroidism. In these instances, there exists a continual risk of the patient's condition advancing to overt hypothyroidism [17].

2. Vitamin D

Vitamin D, a lipophilic vitamin, is crucial for the regulation of calcium in the body and the maintenance of skeletal health. Vitamin D exists primarily in two forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is present in certain plant foods, whereas vitamin D3 is produced in the skin when exposed to direct sunlight [18]. Factors contributing to vitamin D insufficiency include advanced age, female gender, winter months, obesity, malnutrition, insufficient sunlight exposure, and increased skin pigmentation [19]. Vitamin D (VD) is thought to positively influence endothelial cell dysfunction [20], glucose tolerance, cardiovascular health and complications, avert diabetes mellitus (DM), regulate immunity in patients with autoimmune illnesses (such as rheumatoid arthritis and chronic lupus), and promote remission and prevention of multiple sclerosis. The widespread significance of vitamin D may be attributed to the nearly unlimited expression of the VDR (vitamin D receptor) in all organs and tissues of the body[21].

2.1 Physiological action of vitamin D

Both kinds of vitamin D undergo hydroxylation to produce (25(OH)D), or calcidiol, which is the primary circulating form of vitamin D that has a half-life of two to three weeks [22]. A measurement of 25(OH)D is used as a marker to determine the body's vitamin D levels. The primary hydroxylation occurs in the liver, followed by a secondary hydroxylation in the kidney, mediated by 1-α-hydroxylase (CYP27B1), which converts calcidiol into calcitriol, the biologically active form of vitamin D [23]. In target tissues, $1,25(OH)_2D$ interacts with the nuclear vitamin D receptor (VDR) [24], thereby influencing the expression of more than 200 genes, accounting for 3–5% of the human genome [25]. Contrary to previous belief, the enzymes CYP27B1 and VDR are present in almost all body cells, including thyroid and immune cells, not only in skeletal, small intestinal, and renal cells [26]. A membrane-bound version of VDR also occurs, which mediates immediate, non-genomic effects of $1,25(OH)_2D$ [27].

2.2 Vitamin D and Thyroid Autoimmunity—Molecular Mechanisms

Low vitamin D levels and genetic mutations in the VDR gene have been linked to several conditions, such as neurodegenerative diseases, neurodevelopmental diseases, elderly frailty, and, most specifically, autoimmune diseases. The presence of VDR in virtually all immune cells, including neutrophils, macrophages, activated CD8+ and CD4+ T lymphocytes, B lymphocytes, and dendritic cells, suggests that vitamin D plays a role in regulating innate and adaptive immune responses. It has been reported that vitamin D inhibits the synthesis of inflammatory cytokines IL-1, IL-6, IL-12, and TNFα, while simultaneously increasing the generation of interleukin-10, which is

an anti-inflammatory cytokine by monocytes. Additionally, it has been shown to modulate dendritic cell differentiation and maturation. 25OHD can also support the activity and proliferation of immune-suppressive Treg cells and contribute to the Th1/Th2 balance, hence mitigating inflammation and autoimmunity processes. It is crucial to note that this vitamin affects the actions of Th17 cells, an important T cell subtype in autoimmunity. Specifically, it inhibits the release of pro-inflammatory cytokines, including INF-γ, IL-2, IL-17, and IL-21. In this regard, the inhibition of the Th1 response by 25OHD may delay the onset of GD, as Th1 cells play a predominant role in its induction. B lymphocyte proliferation and their differentiation into plasma cells, immunoglobulin production (IgM and IgG), formation of memory cells, and B cell apoptosis are all suppressed by vitamin D [28]. The notable correlation between VDR polymorphism and AITD suggests a possible involvement of vitamin D in their development. In a meta-analysis, Wang et al. identified a significant correlation between autoimmune thyroid disorders and VDR gene polymorphisms in multiple ethnic groups [29]. Furthermore, additional evidence supports the correlation between autoimmune thyroid disease and vitamin D.

Scientific GaP and Objective of Study: While numerous studies support an association between low serum vitamin D levels and autoimmune thyroiditis (AITD), a clear causal relationship remains unconfirmed. Despite evidence of an inverse correlation between 25(OH)D levels and thyroid autoantibody titers, it remains unclear whether vitamin D deficiency is a contributory risk factor, a consequence of autoimmune thyroid dysfunction, or merely a correlational finding.

The study aims to gain a better understanding of the reality of the relationship between vitamin D deficiency and AITD. In addition to its potential contribution to the progress of the condition and strategies for management.

3-Methodology Section

3.1 Search strategy and inclusion criteria:

A search for publications available in online databases (PubMed, Google Scholar, CrossRef) from September to December 2024 was undertaken using a set of keywords: (autoimmunedisease, thyroid, Hashimoto's condition, vitamin D, anti-TPO). Figure (1) shows a flow chart displaying the process of selection for eligible studies.

3.2 Inclusion criteria

The primary inclusion criteria were as follows:

- Articles focusing on autoimmune thyroid disorder
- Studies in the English language
- Available completed data
- Articles to which full access has been granted
- Human studies

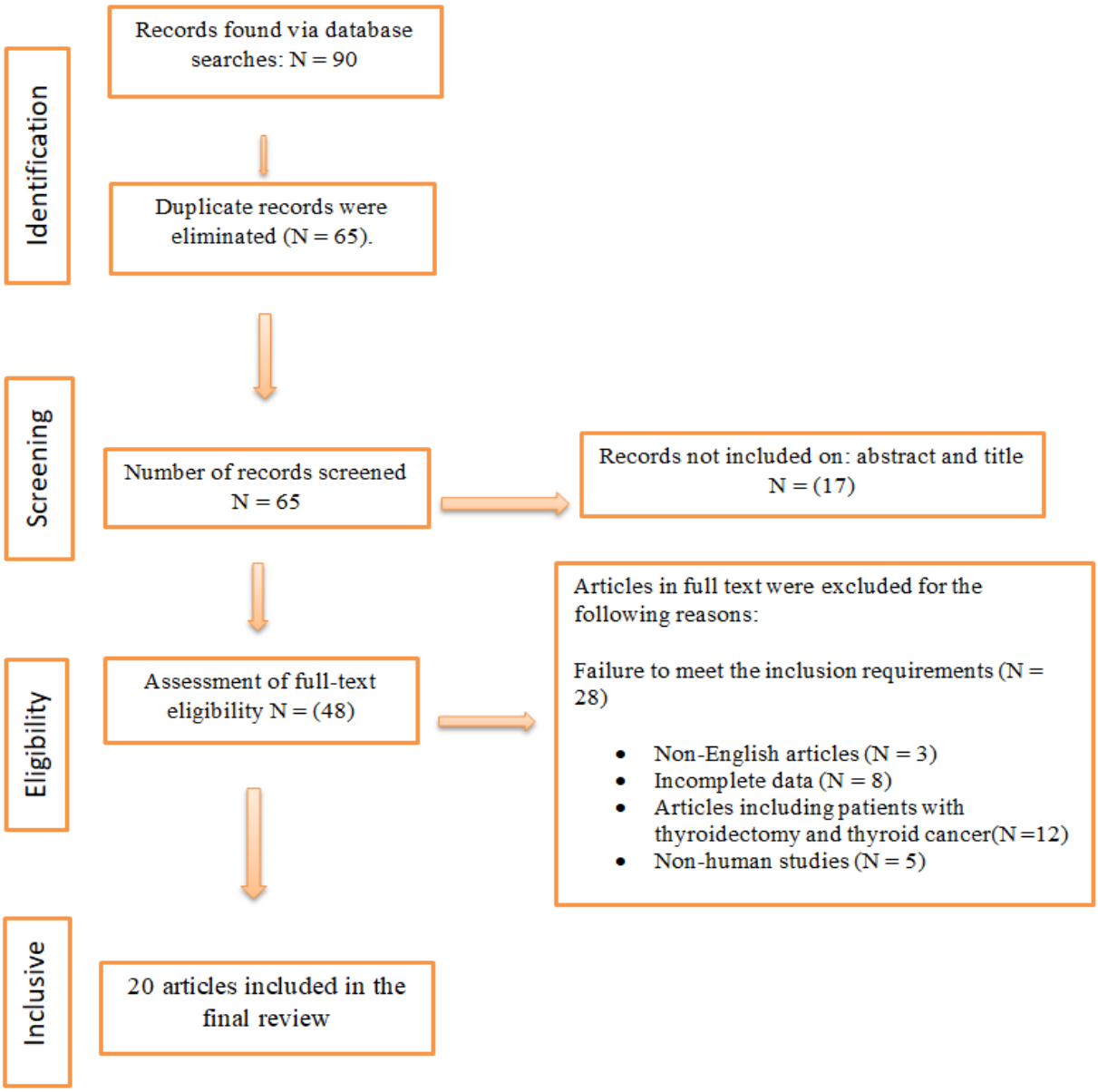

Figure 1. The flowchart illustrates the study's selection process.

4- Results and Discussion

1. Data on the prevalence of hypothyroidism relative to hyperthyroidism:

Hypothyroidism is a common pathological condition worldwide characterized by the inability of the thyroid to synthesize and secrete a sufficient amount of thyroid hormones. Because hormone deficiencies negatively affect the body's overall health, many studies have documented the extent of the disease's spread across regions worldwide. In Al-Nasiriyah city/Iraq, the proportion of hypothyroidism patients to hyperthyroidism patients was (61.84%; 38.16%), P>0.05 by Chase et al. [30]. Similar results were obtained by other authors, Zoori and Mousa [5]; Falgoos and Abdulredha [31], who found that hypothyroidism patients (68.75%, 70.53%), while hyperthyroidism patients (31.25%, 29.46%), respectively. While in an Indian study conducted by Baite et al. [32], who found the proportion

of hypo to hyperthyroidism was (70.83%; 29.17%) with a p-value > 0.05. All these findings revealed that patients with hypothyroidism predominated among thyroid diseases.

Geographically, thyroid diseases are more prevalent in regions with iodine deficiency. Reduced thyroid hormone synthesis and increased incidence of hypothyroidism are linked to inadequate iodine intake [33]. Iodine deficiency and excessive iodine intake can lead to adverse health effects [34, 35]. An excess of iodine impairs thyroid hormone production in vulnerable individuals, leading to increased TSH secretion and possible goitre formation. Nutritional practices, including a vegan diet and little intake of iodine-rich foods, lead to iodine deficiency [36].

2. With respect to gender and age data:

More studies suggest that most patients are women in their thirties and forties. This trend highlights a potential correlation between age, gender, and the prevalence of thyroid disorders. Several results of studies conducted across various Iraqi provinces by several authors, such as Abdullah et al. [37], in Amara city showed in a study consisting of 100 persons (50 patients and 50 as control) aged between 9 and 50 years old that the age group 41-50 years old was the most impacted age group by AIT (46%); then came the cohort aged 31-40 years old (26%), P=0.024. Regarding gender, 82% of patients were women and 18% were males, P=0.01. While Zoori and Mousa [5], in Al-Nasiriyah city, found that females with hypothyroidism were more than males (77.5% vs. 22.5%, respectively), the ratio was 3.4:1, with the highest percentage of patients in the cohort (both hypo and hyperthyroidism) occurring in the age bracket of 36-45 years (38.47% and 40%, respectively).

In Erbil city, Amin et al. [38] found that among 115 patients with thyroid dysfunction, 80% were females vs. 20% males. A distinct age-dependent rise in the prevalence of autoimmune thyroid patients was seen in comparison to healthy individuals, with the highest proportion of affected patients occurring in the 30-39 age bracket, around 35.60%. In the same study, 800 patients with confirmed thyroid disease were included, with 88.7% being women were women and 11.3% being men. Regarding age, 58.5% of the study sample's patients were aged 21-40 years, and 19% were aged 41-50 years, according to Al Barzanji et al. [39]. Similar findings were found in Jantikar's study in India[40], which included 100 patients; their ages were under 18 years old. They were as follows: the majority, 32 patients, were in the 21-30 age group, followed by 24 patients in the 31-40 age group. The ratio of females to males was 2.12:1, including 32% males and 68% females. Another study was conducted in Libya by Mohammed and Asmeil [41] on 515 serum samples from individuals aged 12-98 years. The majority of gender who usually complained of symptoms of thyroid illnesses were females, comprising 86.6% (n=446), whilst males constituted only 13.4% (n=69) of total cases. According to the age factor, the majority of participants were aged between 21 and 30, 30 and 41, and 41 and 50, with the most significant percentages being 23.5%, 23.8%, and 26.5%, respectively.

According to the findings above, middle-aged and elderly people—especially women—show more sensitivity to thyroid problems. Thyroid disorders are widespread around the world, especially among women. This relationship is connected to a disruption in female sex hormones, particularly increased estrogen during pregnancy and puberty.

Inactivation of the X chromosome also influences the immune system and the thyroid gland's activity, making women more likely to get autoimmune thyroiditis [42].

On the other hand, thyroid autoimmunity generally escalates with age, as age-related alterations in bodily functions can influence hormone synthesis, metabolism, tissue responses, and biological rhythms, including the menstrual cycle. Moreover, people with concomitant autoimmune disorders such as type I D.M., rheumatoid arthritis, and multiple sclerosis exhibit a heightened propensity for thyroid dysfunction [43].

3. Estimation of Antibodies against TPO and TSHR in Studied Groups:

The human Auto Immune Thyroid Diseases (AITD) (broadly involving Graves' disease (GD) and Hashimoto's thyroiditis (HT) are hallmarked by the influx of lymphocytes into the thyroid parenchyma and the subsequent generation of autoantibodies against thyroid peroxidase (TPOAb), thyroglobulin (TGAb), or thyrotropin (TRAB) [44]. According to several studies, the pathophysiology and development of hypothyroidism are most closely linked to anti-TPO Ab [45]. While the autoimmune production of TRAb is central to the pathogenesis of GD [46]. In Iraq, frequent studies have assessed the potential impact of anti-thyroid autoantibody levels in AITD, including Abed et al. [47], who found in their study, which consists of 3 groups (GD group n=82, HT group n=78, HC group n=85). The individuals with GD and AIH had higher concentrations of TPOAb (833.99±77.25 IU/m), (911.52±93.65 IU/m), P<0.0001, respectively, compared to HC (23.54±2.39 IU/m). TRAB concentrations were significantly high in GD (15.05±0.98 IU/m), P<0.0001, compared with HC (0.54±0.094 IU/m), while there was no significant difference in HT (0.54±0.09 IU/m). The TPO is a highly predictive factor of AITD, due to a high percentage of hypothyroidism patients (80%) being positive, while it was 48% in hyperthyroidism. On the other hand, anti-TSHR was higher in the hyperthyroidism group at 14.28%, indicated by Zoori and Mousa [5]. Kawther et al. [48] reported the same results, demonstrating that the prevalence of anti-TPO was lower in patients with hyperthyroidism (33.3%) compared to those with hypothyroidism (63.6%). Furthermore, more studies have been performed in different countries regarding this relationship, including a study carried out by Falkowski and his team [49], which included a control group of 72 healthy subjects, 45 participants diagnosed with GD, and 22 with HT. The value of anti-TPO in the form of median was 192 (31-310) U/mL in Graves' disease and 600 (283-600) U/mL (P < 0.001) in Hashimoto's thyroiditis compared with control subjects 12 (9-16). The result of (TRAB) was highly significant at 9.24 (6.05-18.01) U/L (P<0.001) in GD compared with control 0.3 (0.19-0.49), but there was no significant 0.3 (0.22-0.92) U/L in HT. The primary characteristics of AITD are lymphocytic infiltration, autoimmune antibody synthesis, and dysregulation of thyroid-related hormones. Xu et al. [50] reported that TPOAb levels were heightened in individuals with GD and HT (846.8 ± 971.0 IU/m and 930 ± 1006.0 IU/m), P < 0.0001, respectively, compared with healthy controls (0.3 ± 0.2 IU/m). TRAb concentration was significantly elevated in patients with GD (15.2 ± 16.4 IU/m), P>0.0001, compared with controls (0.4 ± 0.2 IU/m), while it was not significant in HT (0.4 ± 0.4 IU/m). Therefore, measuring these thyroid-related parameters may help in the differential diagnosis between GD and HT. Weng et al. [51] found analogous findings in their study, which included 48 HT, 50 GD, and 45 healthy controls (HC), where TPOAB concentration was 926.90 ± 10 IU/m in HT and 846.80 ± 971.00 IU/m in GD with P < 0.0001 compared to HC (0.32 ± 0.24 IU/m). TRAB concentration was significant (16.16 ± 15.35 IU/m) in GD (P < 0.0001) compared with HC (0.35 ± 0.18

IU/m), while there was no significant difference (0.40 ± 0.43 IU/m) in HT. A research study by Sultana et al. [52] comprised 85 patients (55 with hypothyroidism and 30 with hyperthyroidism). The prevalence rate of TPOAb was 54.54% (30 out of 55) in hypothyroid patients and 53.33% (16 out of 30) in hyperthyroid patients.

Key features of AITD include lymphatic infiltration, production of autoantibodies, and disruption of thyroid hormone regulation [13][14]. From the above-presented results, we concluded that patients with GD had higher TRAB concentrations (TRAB is a specific biomarker of GD and aids in the differential diagnosis of hyperthyroidism). In contrast, TPOAB concentrations were raised in both patients with Hashimoto's and Graves' disorders. Autoimmune thyroid disease encompasses several forms, each characterized by distinct signs, symptoms, and requisite therapies. Hashimoto's thyroiditis, an autoimmune condition leading to primary hypothyroidism, requires synthetic T4 for treatment. Graves' disease, caused by an overactive thyroid gland, necessitates the use of anti-thyroid drugs such as propylthiouracil and methimazole [53]. In other words, if thyroid hormone levels are disordered, it is essential to determine if the cause is autoimmune or other thyroid dysfunctions, as they require distinct treatments based on their differing pathogenesis. This can be distinguished using thyroid antibody testing [54].

4. Data regarding Autoimmune Thyroid Disease and Vitamin D Levels:

The impact of serum vitamin D status on AIT remains a subject of extensive investigation. The majority of data indicate a correlation between them. Nonetheless, it remains ambiguous whether vitamin D constitutes simply a correlation or a risk factor in AIT.

Vitamin D insufficiency is prevalent among people with autoimmune thyroiditis (predominantly Hashimoto's disease) [55-64]. Unal et al. [65] observed that individuals with autoimmune thyroid disease exhibited diminished serum vitamin D levels. Also, Hashimoto's thyroiditis (HT) patients exhibit lower levels than those with Graves' disease (GD). Additionally, a negative correlation was identified between anti-thyroid antibody titers and 25(OH)D levels; this result was also reported by additional research [58, 63, 64, 66-74and recently published studies evaluating the effectiveness of vitamin D supplements on autoimmune thyroid disease. After 4 months of receiving oral vitamin D3 (1200–4000 IU/day) in the patient cohort, a significant reduction in serum TPOAb levels was observed [70, 75, 76]. Conversely, some studies contradict the existence of a relationship between both vitamin D and AITD (autoimmune thyroid disorders). D'Aurizio et al. [77] found no statistically significant difference in vitamin D levels between patients with autoimmune thyroid disease (AITD) and healthy controls, and other studies reported the same results [78-80]. Each study mentioned is summarised in Table 1.

Table 1: Results of searches undertaken to assess the influence of vitamin D status and its correlation with thyroid autoimmunity.

Authors	Participants	Key Results	Vitamin D Deficiency Induces AIT
Kim, 2016[55]	407 HC,221 HT, 148 GD	37.1%, 41.9%, and 48.9%of HC, GD, and HT, respectively, exhibited vitamin D deficiency.	+
Unal et al.,2014 [65]	254 HT, 27 GD, 124 HC	25 (OH)D levels were 14.9±8.6 ng/ml in hypothyroidism (HT), 19.4±10.1 ng/ml for Graves' disease (GD), and 22.5±15.4 ng/ml healthy controls (HC); 25OHD exhibited an inverse association with TPOAb (r = –0.176, P=0.003).	+
Evliyaoglu et al., 2015[56]	90 HT; 79 HC	51.9% of HC and 71.1% of HT showed 25OHD insufficiency.	+
D'Aurizio et al., 2015[77]	126 HC,100 AITD	No difference	−
Botelho et al., 2018[78]	71 HC, 88 HT	The two groups exhibited no difference in serum 25OHD levels.	−
Tamer et al., 2011[57]	162 HC, 161 HT	Lack of vitamin D was noted in 91.9% of persons with Hashimoto's and 63% of healthy controls.	+
Shin et al., 2014[66]	111 AITD, 193 non-AITD patients	The average serum 25(OH)D concentration in AIT patients was significantly lower than in non-AITD individuals. (12.6±5.5 ng/ml vs 14.5±7.3, P<0.001; correlation between 25OHD and TPOAb (r = -0.252)).	+
Camurdan et al., 2012[58]	78 HT, 74 HC	Vitamin D deficiency was noted in 73.1% of individuals with HT and 17.6% of healthy controls; an adverse connection between 25OHD and TPOAb was identified (r = -0.3).	+
Metwalley et al., 2016[67]	56 AIT, 56 HC	Compared to the control group, the AIT group's mean vitamin D level was considerably lower (16.2 ± 8.2 vs. 33.9 ± 12.7 nmol/L, P < 0.001). Furthermore, a notable negative connection was seen with TPOAB (r = -0.533).	+

Hosny et al., 2018[68]	60 hypothyroidism group, 30 control group	The serum vitamin D levels of the two groups under investigation exhibited a highly significant difference.: 13.08±3.58 ng/ml in the hypothyroidism group and 20.67±13.33 ng/ml in the control group (P<0.01). Additionally, a significant negative relationship was noted between the serum vitamin D levels and TPOAb (r = - 0.582).	+
Iqbal and Samanje, 2024[69]	60 HT, 30 HC	A significant decline (P<0.01) in mean vitamin D levels was observed in the sick group (10.46 ±3.29) compared to the healthy controls (23.21 ±4.37); a strong negative connection was found between blood 25OHD and TPOAb (r = -0.803, P=0.000).	+
Filipova et al., 2023[79]	57 AITD, 41 HC	No significant difference 73 ±2.8 in AITD, 74.04 ±3.3 in control; P = 0.8	−
Kaur, 2016[59]	40 hypothyroidism, 40hyperthyroidism,40 control	25OHD deficiency was reported to be highest in hypothyroid cases at 62.5%, followed by hyper cases at 47.5%, while the control group had a deficiency of just 40%.	+
Kivity et al. 2011[60]	42 subjects with non-AITDs, 50 subjects with AITDs (22 GD, 28 HT) and 98 healthy subjects were included.	Vitamin D levels were found to be lower in 52% non-AITDs, 72% AITDs (64% GD and 79% HT), and 30% controls.	+
Mackawy et al. 2013[61]	30 people were healthy, and 30 had hypothyroidism	Individuals with hypothyroidism presented a significant prevalence of vitamin D deficiency.	+
Mikulska-Sauermann et al., 2024[62]	81 HT, 34 HC	58.02% of HT had vitamin D deficiency, while 52.94% of HC demonstrated low vitamin D levels.	+
Musa et al. 2017[80]	58 healthy controls, 58 female patients with hypothyroidism.	Vitamin D levels in females with hypothyroidism and healthy controls did not show a significant difference.	−
Chaudhary et al., 2016[75]	112 individuals with AITD	After 8 weeks of vitamin D supplements, a significant decline in anti-TPO concentration was observed.	+

Mazokopakis et al., 2015[70]	218 Greek Caucasian HT patients	An adverse relationship was observed between anti-TPO levels and baseline 25(OH)D. After 16 weeks of vitamin D administration, a significant reduction in TPO antibody levels was observed.	+
Simsek et al., 2016[76]	82 AITD patients	The cohort that received 1000 IU of vitamin D daily for one month reported a significant drop in anti-TPO and anti-Tg titers.	+
Siddiq et al., 2023[71]	72 HT, 72 HC	The mean of serum 25(OH)D was considerably lower in HT at 21.89±3.5 nmol/l than in HC at 42.26 nmol/l (P=0.01); an important association was seen between 25OHD and TPOAb in Hashimoto's patients relative to the control group. Where Hashimoto's anti-TPO increased up to500 mmol/IU.	+
Sönmezgöz et al., 2016[63]	68 children with HT, 68 HC	HT patients had markedly lower 25OHD levels (16.8±9.3 ng/ml) than those of the control group (24.1±9.4 ng/ml, P<0.01).The prevalence of vitamin D insufficiency was 35% in the control group and 76% in the HT group.	+
Xu et al., 2018[72]	200 health control, 194 patients with HT	Concentrations of serum vitamin D were significantly reduced in HT patients at 40.4 (34.3-46.9 nmol/l) compared to controls at 58.3 (52.1-64.8 nmol/l). Vitamin D levels exhibited a negative correlation with TPOAB levels (r = -0.316; P < 0.001).	+
Ma et al., 2015[73]	70 HT, 70 GD, 70 HC	GD, HT subjects had noticeably lower25OHD levels (31.71±13.10 and 31.00±11.15 nmol/l) respectively, compared to control group 41.33±14.48, P<0.001	+
Gierach et al., 2023[74]	134 HT, 125 HC	Anti-TPO and vitamin D demonstrated a slight, negative link in Hashimoto's patients (r = -0.363, P = 0.034), with revealing significantly lower 25(OH)D levels at 27.01±14.4 ng/ml compared to healthy controls (HC) at 34.38±12.6 ng/ml (P<0.001).	+
Giovinazzo et al., 2017[64]	100 newly diagnosed HT patients, 100 HC	The rate of vitamin D depletion in patients with hypothyroidism was markedly greater than in the control group (70% vs 18.2% respectively,	+

	P<0.001). 25(OH)D level was significantly lower in patients with HT (21.2±12.9 ng/ml) compared to the control group (35.7±16.7 ng/ml), p= 0.026; there was a notable inverse association (r = - 0.669, P= 0.034).

25(OH)D: 25-hydroxy-vitamin D; TPOAb: thyroid peroxidase antibody; anti-Tg: thyroglobulin antibody; GD: Graves' disease; HT: Hashimoto's thyroiditis; HC: Healthy control

After the identification of the vitamin D receptor (VDR) in nearly all tissues, new insights emerged elucidating the multifaceted effects and possibly important functions of vitamin D in various extra-skeletal tissues, including those influencing endocrine disorders (Addison's disease, diabetes mellitus, and polycystic ovary syndrome, as well as autoimmune thyroid conditions) [81]. Most studies confirm a relationship between a deficiency of vitamin D and a higher tendency for the formation and/or higher levels of antibodies linked with GD and HT, so the authors suggested that autoimmune thyroid disease is linked with low serum 25(OH)D, where vitamin D deficiency is considered a risk factor for developing the disease. However, it is not an independent one [67]. However, some reports contradict this relationship, complicating the establishment of a unanimous view, which may be attributed to geographical factors, sample sizes, or the methodologies used in these studies.

Because the majority of the studies above support the existence of the relationship. Therefore, the levels of vitamin D, the polymorphisms of the receptor, and the enzyme controlling its metabolism most likely affect its regulatory capacity [82]. Consequently, it plays a role in the evolution of AITD. This contribution probably depends on several other variables, including nutrients, sex hormones, age, and gender [83]. In addition to genetic and environmental factors, these factors may also affect this connection, elucidating some of the inconsistencies in findings across various communities.

5-Conclusion

A large amount of evidence indicates that current data support a possible association between vitamin D deficiency and autoimmune thyroid disease. However, it does not definitively establish that vitamin D is a risk factor. Further large-scale, carefully controlled studies are needed to clarify whether vitamin D plays a causal or therapeutic role in the pathogenesis and treatment of autoimmune thyroid disease. The proper amounts of vitamin D in the body are necessary for ideal thyroid function. Additional research is required to delineate further the pathophysiological mechanisms of thyroid disease and the associated role of 25OHD levels.

Conflicts Of Interest

The authors declare no conflicts of interest.

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