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Critical Review

Vitamin D Deficiency as a Risk Factor for Hypothyroidism: A Revised Evidence-Based Review

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ABSTRACT:

Hypothyroidism is a common endocrine disease characterized by insufficient synthesis of thyroid hormones, which has become a serious health problem worldwide. At the same time, deficiency of vitamin D, an endemic nutritional deficiency is increasingly being associated with a variety of AIDs and endocrinopathies. The aim of this review is to summarize the current literature in relation to vitamin D deficiency and hypothyroidism, with specific

emphasis on immunologic mechanisms and clinical significance. A review of the newer literature (2020-25) was performed, including observational studies, meta-analyses and interventional trials. The findings indicate a notable correlation between decreased serum vitamin D levels and an elevated risk of hypothyroidism., especially autoimmune hypothyroidism like Hashimoto's thyroiditis. Mechanistically, vitamin D exerts immunomodulatory impacts by regulating the balance between T-helper cells, enhancing regulatory T cell activity while inhibiting pro-inflammatory cytokine production, thereby influencing thyroid autoimmunity. Large-scale population studies, comprising the National Health and Nutrition Examination Survey (NHANES), have documented adjusted odds ratios of 1.6 to 1.7 for hypothyroidism in vitamin D deficiency individuals. Meta-analyses support these findings, indicating significantly reduce serum vitamin D levels in hypothyroidism and Hashimoto's thyroiditis patients relative to healthy controls. Vitamin D supplementation has demonstrated potential in lowering thyroid autoantibody levels and enhancing thyroid function in certain studies, the clinical benefits remain heterogeneous and appear to be most effective in euthyroid individuals with baseline vitamin D deficiency. This review concludes that vitamin D deficiency is a significant risk factor for hypothyroidism and highlights the potential of vitamin D supplementation as an adjunctive therapy, especially in population with a high prevalence of both conditions, for instance, in the Middle East and North Africa. To create conclusive clinical guidelines, more extensive randomized controlled trials are required.

KEYWORDS: Vitamin D Deficiency, Hypothyroidism, Immunomodulation, Vitamin D Supplementation.

INTRODUCTION

One prevalent endocrine condition is hypothyroidism defined by insufficient production of thyroid hormones, which slows the body's metabolism. It is expected to affect 4.6% of the US population, with a higher frequency among women and the elderly (Wyne et al., 2023). The condition may present in different manifestations, including overt hypothyroidism with distinct clinical symptoms and subclinical hypothyroidism, distinguished by elevated thyroid-stimulating hormone (TSH) levels in conjunction with normal free thyroxine (fT4) levels (Koulouri and Gurnell, 2013; Sadee et al., 2025). In areas where iodine consumption is sufficient, autoimmune thyroid disease is the main cause of hypothyroidism, particularly Hashimoto's thyroiditis, marked by the immune system's assault on the thyroid gland (Vanderpump, 2011; Appunni et al., 2021; Sadee et al., 2025). Hashimoto’s thyroiditis is defined by lymphocytic infiltration of the thyroid, resulting in an autoimmune-mediated decline in thyroid follicle function. The spectrum of clinical manifestations encompasses a wide range, from normal thyroid function to overt and subclinical hypothyroidism, with or without the presence of goiter (Caturegli et al., 2014; Sun et al., 2025). The clinicopathological forms of Hashimoto’s thyroiditis are defined by the existence of circulating antibodies in opposition to thyroglobulin (Tg) and thyroid peroxidase (TPO). Thyroid hormones (THs), T4 and T3, rely on TPO for their synthesis, while their storage within the thyroid follicles

necessitates Tg (Caturegli et al., 2014; Fröhlich and Wahl, 2017). Hashimoto's thyroiditis exhibits a greater prevalence in females than in males (Huang et al., 2019).

Vitamin D includes a group of lipophilic compounds that are crucial for bone health and the control of the body's phosphorus and calcium levels (Zhao et al., 2021). Vitamin D presented in two primary forms: vitamin D2 (ergocalciferol), sourced from plants, and vitamin D3 (cholecalciferol), synthesized in the skin upon sunlight exposure (Benedik, 2021). The skin uses the enzyme 7-dehydrocholesterol reductase to convert 7-dehydrocholesterol into cholecalciferol when exposed to ultraviolet B radiation from sunshine (Engelsen, 2010; Karakaya et al., 2025). Following synthesis, vitamin D is subjected to 25-hydroxylation in the liver, leading to the production of 25-hydroxyvitamin D [25(OH)D], recognized as a standard measure of circulating vitamin D concentrations. After that, 25(OH)D is carried to the kidneys, where it is further hydroxylated to produce 1,25-dihydroxyvitamin D (calcitriol), the biologically active form (Balachandar et al., 2021). Deficiency of vitamin D constitutes a global health issue, impacting around 41.6% of the US population, with elevated prevalence in specific ethnic groups (4). Deficiency of vitamin D is notably common throughout the Middle East and North Africa (MENA) area, especially Libya, attributable to inadequate sun exposure, dietary practices, and hereditary factors (5)

Vitamin D insufficiency is gaining acknowledgment as a factor affecting thyroid function. Vitamin D regulates the immune system, with its receptors located in thyroid tissue, thereby influencing inflammation and autoimmunity. Studies show that individuals with hypothyroidism frequently exhibit reduced vitamin D levels, which are associated to elevated TSH levels and increased thyroid antibody levels. Although the effects on thyroid hormones are diverse, taking a supplement may help lower autoimmune antibodies and promote thyroid health. Measurement of vitamin D deficiency in thyroid disease is crucial for improving results, as this highlights. Nonetheless, it remains ambiguous whether vitamin D inadequacy contributes to the onset of hypothyroidism or is a resultant effect of the illness. The possible association between vitamin D insufficiency and hypothyroidism has attracted much interest in recent years. This study seeks to deliver a thorough examination of the existing information regarding the relationship between vitamin D insufficiency and hypothyroidism, investigating the underlying mechanisms, clinical ramifications, and possible therapeutic approaches. The results of this review will be especially pertinent to the clinical environment in Tripoli, Libya, where both disorders are expected to be common.

VITAMIN D

METABOLISM AND PHYSIOLOGY

Vitamin D comes in a variety of fat-soluble secosteroid forms (vitamin D1 through D5). The two main types of vitamin D that are important for humans are cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). The majority of vitamin D is synthesized in the epidermis as a result of exposure to sunlight (vitamin D3), whereas only 5–10% is obtained from dietary sources (vitamin D2 and D3) (Dragomir et al., 2024). Dietary sources provide a limited quantity of vitamin D, primarily from egg yolks, fatty fish, and fortified foods, in the forms of vitamin D2 (ergocalciferol) and D3. Upon entering the bloodstream, vitamin D associates with vitamin D-binding protein for transport to the liver. There, it undergoes the initial hydroxylation step, leading to the synthesis of 25-hydroxyvitamin D, which is the predominant circulating form of vitamin D and functions as the most dependable marker of an individual's vitamin D status (Engelsen, 2010; Karakaya et

al., 2025). The concluding hydroxylation step takes place predominantly in the kidneys, wherein 25(OH)D is transformed into its biologically active variant, 1,25(OH)2D, commonly known as calcitriol (Balachandar et al., 2021). In order to control the metabolism of phosphate and calcium, calcitriol subsequently binds to vitamin D receptors (VDRs) in a variety of bodily tissues, like the bones, kidneys, and intestines. In addition to increasing phosphate excretion and calcium reabsorption in the kidneys, calcitriol facilitates the phosphorus and calcium absorption in the intestines. To ensure healthy bone growth and maintenance, calcitriol aids in the control of bone remodeling and mineralization (Matikainen et al., 2021).

The vitamin D receptor functions as a ligand-dependent transcription factor that, upon interaction with 1,25(OH)2D, establishes a heterodimeric complex with the retinoid X receptor (RXR). At the promoter regions of target genes, the complex binds to vitamin D response elements (VDREs), which regulate the transcription of those genes (Zmijewski and Carlberg, 2020; Ghaseminejad-Raeini et al., 2023). The VDR is found in both benign and cancerous thyroid tissues, indicating a direct involvement of vitamin D in thyroid physiology (Conard et al., 2025). Alongside its recognized role in phosphate and calcium regulation, vitamin D is acknowledged for its significant role as an immunomodulatory agent. It is essential to both the adaptive and innate immune systems, affecting the functions of various immune cells like dendritic cells, macrophages, B cells and T cells (Aribi et al., 2023; Srivastava et al., 2025).

Getting vitamin D from sunshine is the best method, but can also be found in meals such as dairy, eggs, fatty fish, and grains (Borel et al., 2015). However, attaining sufficient vitamin D levels exclusively through dietary intake or sunlight exposure poses challenges for numerous high-risk populations, including, but not limited to, persons aged 65 and older, patients with cancer, populations with darker skin pigmentation, syndromes of malabsorption, autoimmune disorders, diabetes, cardiovascular conditions, and individuals with a body mass index (BMI) greater than 30 (Parva et al., 2018; Bleizgys, 2021). Based on a recent aggregated analysis encompassing 7.9 million participants conducted by (Cui et al., 2023), it is predicted that approximately 15.7% of the worldwide population suffers from vitamin D deficiency. Simultaneously, other research suggests that the incidence of vitamin D deficiency in Europe may attain 40%, with severe inadequacy impacting roughly 13% of the population (Amrein et al., 2020).

The Role of Vitamin D in Modulating Immune System Function

Vitamin D exerts its immunomodulatory effects via multiple mechanisms. Vitamin D is instrumental in the prevention of autoimmune processes (Lisowska and Bryl, 2017; Harrison et al., 2020). Vitamin D is vital for the immune system, given that VDRs are found in various peripheral blood mononuclear cells, such as antigen-presenting cells, B cells as well as and T cells (Bizzaro et al., 2017). Calcitriol affects the transcriptional activity of genes related to immune cell function via genomic pathways, regulating processes like the cell cycle, cell differentiation, stress response, programmed cell death, and the fight against infections. Vitamin D could improve the synthesis of antimicrobial peptides, such as cathelicidin antimicrobial peptide LL-37, that compromise the integrity of bacterial and viral cell membranes (Ismailova and White, 2022).

Moreover, vitamin D reduces the expression of co-stimulatory molecules on MHC class II and dendritic cells (DCs), which are key antigen-presenting cells, thereby inhibiting excessive T-cell activation (Ao et al., 2021). Vitamin D inhibits the synthesis of cytokines in dendritic cells while encouraging

the production of cytokines that reduce inflammation, including interleukin 10 (Bscheider and Butcher, 2016). Vitamin D stops helper T cell (Th cell) growth and differentiation in T cells, while promoting their differentiation into Th2 cells, thereby aiding in the maintenance of Th1/Th2 balance (Zhao et al., 2021). Vitamin D inhibits the formation of Th17 cells and promotes the differentiation of regulatory T cells (Tregs), which mitigate autoimmune responses by producing anti-inflammatory cytokines (Cyprian et al., 2019). B cells, responsible for antibody production, also express vitamin D receptor (VDR).

Vitamin D influences B cells in multiple ways, specifically by obstructing the differentiation or maturation of naive B cells into plasma cells, which may consequently decrease autoantibody production (Rolf et al., 2016). The vitamin D immunomodulatory characteristics are particularly significant in autoimmune thyroid disorders, when an aberrant immune response results in the death of thyroid tissue.

Vitamin D's positive impact on the immune system, observed at both cellular and molecular levels, are associated with enhanced clinical results in autoimmune diseases individuals. Multiple observational studies and Clinical research indicates that vitamin D administration may improve the incidence and course of a number of autoimmune diseases, including vitiligo (Karagüzel et al., 2016), rheumatoid arthritis (Chandrashekara and Patted, 2017), and inflammatory bowel disease (El Amrousy et al., 2021).

The VITAL randomized controlled study conducted in 2022, involving 25,871 participants from the United States, showed that 2000 IU as a daily supplementation of vitamin D throughout a five-year span resulted in a 22% reduction in the likelihood of acquiring any autoimmune condition (Hahn et al., 2022).

Numerous meta-analyses have demonstrated that the risk of certain autoimmune diseases, including autoimmune thyroid disease, is increased by vitamin D insufficiency (Taheriniya et al., 2021; Miao et al., 2022; Gorini and Tonacci, 2024; Sultanalieva et al., 2025).

Hypothyroidism: Pathophysiology and Epidemiology

A clinical disease known as hypothyroidism is caused by insufficient thyroid hormone production, primarily triiodothyronine (T3) and thyroxine (T4). The condition may be categorized as primary, secondary, or tertiary, based on the extent of involvement of the hypothalamic-pituitary-thyroid (HPT) axis (Taylor et al., 2024). High thyroid-stimulating hormone (TSH) levels suggest a patient is hypothyroid, with reduced thyroid hormone levels (Clinical Overt primary hypothyroidism), or within the subclinical hypothyroidism reference range. Hypothyroidism is the most common autoimmune disease that affects a large number of adults and occurs due to the production of mucopolysaccharides within the tissues and skin, leading to symptoms such as, cold intolerance, fatigue, and constipation (Wyne et al., 2023). In general, thyroid function decreases with aging; women between the ages of 45 and 64 had a 5.1% prevalence of hypothyroidism, rising to 12.7% in people over 65 (Prados-Torres et al., 2018).

Thyroglobulin (Tg) and thyroid peroxidase (TPO) antibodies are produced as markers of autoimmune thyroid illness, and lymphocytic infiltration is an organ-specific autoimmune disease called Hashimoto's thyroiditis. This condition has emerged as the primary cause of hypothyroidism globally (Khachaturov et al., 2025). Hashimoto's thyroiditis is marked by a Th1-dominant immune response, defined by elevated levels of pro-inflammatory cytokines, including

interleukin-2 (IL-2) and interferon-gamma (IFN-γ) (Wrońska et al., 2024). Research demonstrates that patients with Hashimoto's thyroiditis frequently display diminished vitamin D levels relative to healthy counterparts, implying a possible association between vitamin D insufficiency and the onset of autoimmune thyroid conditions (Hu and Rayman, 2017). It is thought that the VDR, which is expressed in different types of immune cells, mediates the immunomodulatory effects of vitamin D (Bikle and Christakos, 2020).

This interactive influences T cell development and function, fostering an anti-inflammatory milieu and possibly diminishing the autoimmune assault on thyroid tissue. Vitamin D levels have been shown to rise the activity of regulatory T cells and inhibits the generation of pro-inflammatory cytokines (Minton, 2022), that are essential for preserving immunological tolerance (Durá-Travé and Gallinas-Victoriano, 2024).

The incidence of hypothyroidism differs among various groups and is affected by factors like age, sex, iodine consumption, and genetic susceptibility, with elevated rates noted in women. About 4.6% of the population in the US suffers from hypothyroidism, with a greater incidence among women and the elderly. Elevated TSH levels with normal free T4 levels constitute subclinical hypothyroidism, which affects as many as 10% of the population (Wyne et al., 2023). The incidence of hypothyroidism is notably elevated in the Middle East and North Africa (MENA) region, however data from Libya remains scarce. A study conducted in Egypt indicated a prevalence of 7.7% for hypothyroidism among 7,943 people (Appunni et al., 2021). The significant frequency of hypothyroidism and vitamin D insufficiency in the MENA region highlights the necessity of exploring the potential correlation between these two diseases.

Mechanisms Linking Vitamin D Deficiency and Hypothyroidism

Because it controls both innate and adaptive immunological responses, vitamin D has a major impact on the immune system. It boosts the ability of monocytes and macrophages to fight against infections by encouraging the creation of peptides that are antimicrobial, such as defensins and cathelicidin. Vitamin D also affects T cell differentiation and function by blocking Th1 and Th17 cells, which are pro-inflammatory, from activating, while augmenting regulatory T cells that facilitate immune tolerance. The immunomodulatory impact is substantial in autoimmune disorders, as vitamin D deficiency correlates with heightened disease severity and activity. In addition to being necessary for healthy immune function, vitamin D levels may help prevent infections and a number of autoimmune diseases (Siddiq et al., 2023; Mikulska-Sauermann et al., 2024; Sun et al., 2025).

(Zhao et al., 2021) identified four potential mechanisms through which Vitamin D may Inhibit the immune response in HT. (1) Inhibition of dendritic cell-mediated T-cell activation; (2) Reduction in the thyroid's expression of the HLA class II gene; (3) Impact on B-cell function; and (4) Reestablishment of the Th17/Treg balance.

T-helper cell differentiation regulation is a fundamental immunological mechanism. The development of naive T cells into regulatory T cells (Tregs) is aided by vitamin D, which possess immunosuppressive functions and support the preservation of immune tolerance. In contrast, T-cell differentiation into pro-inflammatory T-helper 17 (Th17) and T-helper 1 (Th1) cells is inhibited by vitamin D (Zhao et al., 2021). Hashimoto's thyroiditis is characterized by a Th1-dominant immune response, marked by elevated pro-inflammatory cytokines levels, comprising IFN-γ and IL-2 (Wrońska et al.,

2024). A lack in vitamin D can intensify the Th1-dominant response, resulting in heightened inflammation and tissue damage within the thyroid gland. Research indicates that vitamin D insufficiency impairs the VDR-mediated equilibrium between Tregs and Th17 cells, resulting in a 40-60% elevation in anti-TPO antibody titers and an augmented risk of hypothyroidism development (Sun et al., 2025).

The modulation of B cell function by vitamin D represents another significant mechanism. B cells produce antibodies, including the autoantibodies characteristic of Hashimoto's thyroiditis. Vitamin D inhibits the proliferation of B cells and transforming into plasma cells, which reduces the production of immunoglobulins and autoantibodies (Lebiedziński and Lisowska, 2023). In Hashimoto's thyroiditis individuals, a deficit in vitamin D correlates with increased anti-thyroglobulin and anti-TPO antibody levels. Vitamin D supplementation has demonstrated a reduction in autoantibody levels, indicating a direct influence of vitamin D on B cell functionality (Tang et al., 2023).

Besides its immunomodulatory effects, vitamin D may also influence thyroid hormone synthesis and secretion. The VDR is present in thyroid follicular cells, and its activation by 1,25(OH)2D can influence the proliferation, differentiation, and functional activity of these cells (Wu et al., 2025). Studies show that vitamin D plays a role in increasing the expression of genes related to thyroid hormone production, including the thyroglobulin and sodium-iodide symporter (NIS). Moreover, vitamin D could exert a direct influence on the hypothalamic-pituitary-thyroid (HPT) axis. Certain research has indicated that vitamin D may influence the regulation of TSH secretion from the pituitary gland, though the precise mechanism remains inadequately elucidated (Sahi et al., 2025).

A lack of vitamin D has been associated with autoimmune thyroid disease and other autoimmune disorders, comprising diabetes mellitus, multiple sclerosis systemic and lupus erythematosus (Jiang et al., 2023). 1α-hydroxylase and VDR are present in immune cells such as neutrophils, B and T lymphocytes, monocytes and dendritic cells (Bui et al., 2021). Consequently, these cells are capable of synthesizing calcitriol, the active vitamin D3 form. Vitamin D influences the function of certain immune system cells and contributes to immune system control. Vitamin D suppresses the synthesis of proinflammatory cytokines, such as IFN-γ, TNF-α, IL-8, IL-6, IL-12, and IL-9. It additionally increases the synthesis of anti-inflammatory cytokines, including IL-5, IL-10, and IL-4. It is believed that vitamin D has an anti-inflammatory impact (Bui et al., 2021). (Feng et al., 2020) found that HT had a positive correlation with antithyroid antibodies in Chinese children with blood IL-21 levels, whereas there was a substantial inverse relationship between serum IL-21 and serum 25(OH)D levels. The investigators indicated that the findings suggest a potential involvement of IL-21 and vitamin D levels in the occurrence and progression of HT.

Despite the substantial study that has been done to elucidate the part of vitamin D in the etiology of autoimmune thyroid diseases, whether vitamin D insufficiency is a significant contributing element to their etiology or just a result of these disorders is still unknown (Babić Leko et al., 2023).

The relationship between hypothyroidism and vitamin D is further influenced by both genetic predispositions and environmental influences. Variations in the vitamin D receptor (VDR) gene have been connected to a heightened susceptibility to autoimmune thyroid diseases, indicating that genetic differences in the VDR may influence the reaction of the body to vitamin D (Maciejewski et al., 2019; Majid et al., 2024).

Environmental factors, including solar exposure, dietary vitamin D intake, and lifestyle decisions, can influence vitamin D

status and, subsequently, the risk of hypothyroidism. The high incidence of vitamin D insufficiency in the MENA region, particularly in Libya, is due to a number of reasons, including genetic predisposition, dietary habits, and restricted sun exposure resulting from cultural practices, (Alalem et al., 2022; Machuron et al., 2025).

Clinical Evidence: Observational Studies

The link between hypothyroidism and vitamin D insufficiency has been extensively studied using a variety of observational methods, such as case-control, cohort, and cross-sectional studies. These studies have consistently documented a strong correlation between reduced serum vitamin D levels and an increased risk of hypothyroidism, especially autoimmune hypothyroidism. The most extensive and exhaustive of these investigations is the National Health and Nutrition Examination Survey (NHANES), that provides a sample of the US population that is nationally representative. Hypothyroidism was detected in 614 (7.7% of the total) of the 7,943 adults aged 20 and up in the NHANES investegate by (Appunni et al., 2021). Deficiency in vitamin D was more common in hypothyroid patients (25.6% vs. 20.6% overall) according to the research. The study indicated that, after accounting for potentially confounding variables such age, sex, race, BMI, and comorbidities, the adjusted odds ratios (aOR) for intermediate vitamin D levels were 1.7 (95% CI: 1.5-1.8) and for inadequate levels, they were 1.6 (95% CI: 1.4-1.9). According to these results, hypothyroidism is more prevalent among individuals whose vitamin D levels are low.

A meta-analysis and systematic review carried out by **(Taheriniya et al., 2021)** supported these findings by aggregating data from various observational studies. The meta-analysis encompassed research on HT, AITD, and hypothyroidism. The results demonstrated that patients with AITD had much lower serum vitamin D levels (WMD: −3.1 ng/dl; 95% CI: −5.57 to −0.66; P = 0.013), hypothyroidism (WMD: −13.43 ng/dl; 95% CI: −26.04 to −0.81; P = 0.03), and Hashimoto's thyroiditis (WMD: −6.05 ng/dl; 95% CI: −8.35 to −3.75; P < 0.001) compared to healthy controls. The substantial heterogeneity (I^2 > 90%) observed among the included studies indicates variability in the association across diverse populations and study designs, although the overall trend remains consistent.

Multiple case-control studies have reported analogous findings. (Ke et al., 2017) conducted research that compared serum vitamin D levels in Hashimoto's thyroiditis and Graves' disease patients, finding significantly reduced Hashimoto's cohort vitamin D levels.

The relationship between insufficient levels of vitamin D and the occurrence of hypothyroidism has been observed across various populations, including individuals with type 2 diabetic mellitus (T2DM). (Wu et al., 2025) conducted a study examining data from 1,805 persons with T2DM, revealing that vitamin D insufficiency was independently linked to hyperthyroidism and subclinical hyperthyroidism. The research indicated that vitamin D sufficiency exhibited a positive correlation with male gender, advanced age, and elevated free triiodothyronine (FT3) levels, whereas it exhibited an inverse relationship with increased triglycerides and HbA1c levels.

A 2025 Pakistani case–control study involving 400 participants revealed that 85.3% of individuals with autoimmune thyroid disease exhibited vitamin D insufficiency or deficiency, in contrast to 55.5% of non-AITD subjects. Furthermore, low 25(OH)D was independently exhibited a positive correlation with AITD and elevated TSH subsequent to adjusting for age, sex, body mass index, and seasonal variations (Rasool et al., 2025). Moreover, a study by (Alqurieny et al., 2025) compared autoimmune and non-autoimmune hypothyroidism, revealing that both groups

demonstrated markedly reduced levels of 25(OH)D relative to the reference values of a healthy population, with the most diminished vitamin D levels are observed in cases of autoimmune hypothyroidism and an inverse connection between 25(OH)D and TSH. The data indicate that hypovitaminosis D is predominantly concentrated in autoimmune conditions, however it is equally prevalent among non-autoimmune hypothyroid patients.

Notwithstanding the consistent results from observational research, it is crucial to acknowledge that these studies cannot determine causality. The identified relationship between hypothyroidism and vitamin D deficiency may result from reverse causation, wherein hypothyroidism induces vitamin D deficiency, or from confounding variables such as obesity, sedentary behavior, and dietary practices. The biological plausibility of the connection, bolstered by previously stated immunomodulatory and hormonal pathways, suggests that hypothyroidism may be caused by a vitamin D deficiency.

Clinical Evidence: Interventional Studies

Despite observational research have showed a notable connection between hypothyroidism and vitamin D deficiency, interventional studies are essential to determine if vitamin D therapy may enhance thyroid function and lower the risk of hypothyroidism. An increasing number of randomized controlled trials (RCTs) and clinical trials have examined the supplementation vitamin D impact on thyroid function parameters, autoantibody concentrations, and clinical outcomes in individuals with hypothyroidism and autoimmune thyroid disorders. Where, one potential immunomodulatory strategy for Hashimoto's thyroiditis is vitamin D therapy, there is increasing evidence that it can lower levels of thyroid autoantibodies, especially thyroid peroxidase antibodies (TPOAb), in a subset of patients.

Numerous randomized controlled studies have indicated that administration of vitamin D may decrease levels of thyroid autoantibodies, especially anti-thyroid peroxidase (TPO) antibodies. A meta-analysis of randomized controlled studies including patients with Hashimoto’s thyroiditis revealed that treatment of vitamin D significantly elevated serum 25(OH)D levels and resulted in a modest yet notable reduction in TPOAb titers relative to the control group, with no discernible impact on TSH, FT3, or FT4 levels (Hui et al., 2022). A thorough evaluation and meta-analysis carried to assessed the effect of thyroid function and supplementation of vitamin D on autoantibodies in Hashimoto's thyroiditis individuals (Tang et al., 2023). The meta-analysis incorporated data from various RCTs and determined that supplementation of vitamin D markedly reduced TPO antibody levels, having an average discrepancy of -15.3 IU/mL (95% CI: −25.6 to −5.0; P = 0.004). The research indicated that supplementation of vitamin D positively influenced thyroid function, demonstrated by reduced levels of TSH and elevated levels of fT4.

A separate randomized controlled trial performed to study the supplementation of vitamin D impact on levels of TSH and thyroid hormone in subclinical hypothyroidism individuals (Safari et al., 2025). In contrast to the placebo-treated control group, the intervention group experienced a notable drooping in TSH levels and a raise in fT4 levels after taking vitamin D supplements (2000–4000 IU/day) for 12 weeks. Although the result did not achieve statistical significance, the study also found that the vitamin D treatment group had lower levels of anti-TPO antibodies. These results imply that people with subclinical hypothyroidism may benefit from vitamin D therapy in terms of thyroid function.

Nonetheless, not all interventional studies have yielded positive findings. A study performed by (Knutsen et al., 2017) employed

a randomized, double-blind, controlled study involving ethnic minorities with a reduction in vitamin D levels and observed no substantial effect in supplementation of vitamin D on levels of thyroid function or thyroid autoantibody. The study encompassed participants from the Middle East, South Asia, and Africa, and the findings demonstrate that the impact of vitamin D supplementation may vary between different ethnic groups. Another study carried out by (Mirhosseini et al., 2017) showed that physiological serum vitamin D levels were correlated with enhanced thyroid function; however, the study did not find a notable impact of vitamin D supplementation on thyroid hormone levels in overt hypothyroidism patients.

The variability in outcomes of interventional studies can be ascribed to several variables, like the dosage and length of vitamin D supplementation, the participants' initial levels of vitamin D, and the existence of additional comorbidities. (Sun et al., 2025) emphasized the significance of genotype-guided dosing in vitamin D supplementation, noting that genetic variations in the reaction to vitamin D could be affected by the VDR gene. The review highlighted the necessity for personalized medicine strategies, given that the therapeutic window for vitamin D supplementation seems restricted to euthyroid individuals who exhibit a baseline deficiency in vitamin D.

Two studies in a 2025 systematic review on vitamin D in Hashimoto’s thyroiditis concluded that supplementation often results in a notable drooping in TPOAb and/or TgAb across various populations, although effect sizes and responder rates differ (Karakaya et al., 2025; Luo et al., 2025). However, the latter study emphasized considerable variability in dosing regimens and initial vitamin D status.

Besides its impact on thyroid function, vitamin D supplementation may significantly influence surgical outcomes in individuals with Hashimoto's thyroiditis. (Yang et al., 2025) identified that vitamin D deficiency independently predicts postoperative hypocalcemia and hypothyroidism in patients undergoing thyroidectomy for Hashimoto's thyroiditis. The study advised preoperative enhancement of vitamin D levels (25(OH)D >30 ng/mL) to mitigate the risk of postoperative problems. The data indicate that vitamin D administration could improve thyroid function and mitigate surgical risks in autoimmune thyroid disorders patients.

Special Considerations: Regional Perspectives

The relationship between hypothyroidism and vitamin D deficiency is especially significant in the MENA region, comprising Libya, where both conditions are widespread. The MENA region exhibits one of the highest prevalences of vitamin D deficiency globally, with rates spanning from 50% to 80% among certain populations (Hussein et al., 2022; Cui et al., 2023). In this area, the notable frequency of vitamin D deficiency results from various factors, such as restricted sun exposure linked to genetic predisposition dietary habits, and cultural practices. Women in the MENA region face heightened risks due to cultural norms that necessitate skin covering and restrict outdoor activities, consequently diminishing their sunlight exposure (Bassil et al., 2013).

The prevalence of hypothyroidism in the MENA region is notably high, although data from Libya remains limited. A study conducted in Egypt indicated a hypothyroidism prevalence of 7.7% among a sample of 7,943 adults (Appunni et al., 2021). A new investigation conducted in Algeria indicated that compared to healthy controls, individuals with hypothyroidism were more likely to have vitamin D deficiency, and it was found to be linked to increased concentrations of anti-TPO antibodies (Meghelli et al., 2024). The findings indicate that the correlation between hypothyroidism and vitamin D insufficiency

extends beyond Western populations, demonstrating significance in the MENA region as well.

The widespread occurrence of both vitamin D deficiency and hypothyroidism in the MENA region has substantial ramifications for public health and clinical management (Machuron et al., 2025). The simultaneous presence of these two conditions may exacerbate the disease burden in the region and could have implications for the management of both conditions. For instance, patients with hypothyroidism who are concurrently deficient in vitamin D may necessitate higher doses of levothyroxine to attain appropriate thyroid hormone replacement, as vitamin D deficiency can influence the absorption and thyroid hormones metabolism (Ashok et al., 2022).

The high incidence of vitamin D insufficiency in the MENA area underscores the necessity for public health interventions to tackle this concern. Assessment for widespread vitamin D insufficiency particularly susceptible groups, such as pregnant women and women of childbearing age, and autoimmune diseases individuals, may substantially reduce the long-term risk of hypothyroidism and other conditions linked to vitamin D insufficiency (Appunni et al., 2021).

Public health campaigns aimed at promoting vitamin D dietary intake, sun exposure, and supplementation of vitamin D could be effective in decreasing the region's prevalence of vitamin D insufficiency.

The significant occurrence of vitamin D insufficiency and hypothyroidism in Tripoli, Libya indicates a necessity for targeted screening and intervention programs. The clinical environment in Tripoli could improve through the adoption of vitamin D screening protocols for autoimmune thyroid disorders individuals and hypothyroidism.

The supplementation of vitamin D incorporation in the treatment of hypothyroidism may enhance clinical results and decrease the likelihood of complications. Additional research is required to determine the best dose and length of vitamin D administration in the Libya's populace, along with an assessment of the prolonged impact on thyroid function and autoimmune markers.

Clinical Implication and Recommendations

The expanding body of research associating vitamin D deficiency with hypothyroidism has significant consequences for therapeutic practice. Consistent evidence from observational studies, meta-analyses, and interventional trials demonstrate that vitamin D insufficiency constitutes a significant predisposing factor for hypothyroidism, particularly autoimmune hypothyroidism. This has prompted requests for the incorporation of vitamin D screening and supplementation into the treatment of autoimmune and hypothyroidism thyroid disease.

Vitamin D insufficiency should be prioritized as a public health intervention, particularly in high-risk groups like women, older adults, and those with autoimmune diseases (Machuron et al., 2025).

The necessity for routine screening of vitamin D levels in autoimmune thyroid diseases and hypothyroidism patients is a significant clinical implication. Owing to the considerable incidence of inadequate vitamin D in these demographics, it is recommended to include assessment for vitamin D insufficiency as a standard component of the initial evaluation for patients with hypothyroidism. Serum 25-hydroxyvitamin D measurement serves as the most dependable metric of an individual's vitamin D status and is recommended for all patients with hypothyroidism, especially those with autoimmune thyroid disease (Sun et al., 2025).

For individuals identified as vitamin D deficient, supplementation of vitamin D ought to be considered as an adjunctive therapy. The

precise optimal dosage of vitamin D supplementation for individuals with hypothyroidism remains undetermined; nevertheless, numerous studies indicate that doses ranging from 2000 to 4000 IU per day may effectively diminish thyroid autoantibody levels and enhance thyroid function (Sun et al., 2025). The supplementation period must be a minimum of 3-6 months to facilitate a substantial decrease in autoantibody levels and enhancement of thyroid function. Monitoring serum 25(OH)D levels during supplementation is crucial to obtain the target level of >30 ng/mL, which is linked to good immune function and a diminished risk of autoimmune disorders (Tang et al., 2023).

The supplementation of vitamin D benefits is likely most significant in euthyroid people exhibiting baseline vitamin D insufficiency and positive thyroid autoantibodies. A review by (Sun et al., 2025) underscored the importance of genotype-guided dose in vitamin D supplementation, as genetic differences in the reaction to vitamin D may be influenced by the VDR gene. The review highlighted the necessity for personalized medicine strategies, given that the therapeutic window for vitamin D supplementation seems restricted to euthyroid individuals who have a baseline deficiency in vitamin D. In manifest hypothyroidism patients, the supplementation of vitamin D efficacy may be restricted, as the autoimmune process may have advanced to a stage where such supplementation is ineffective.

Besides its influence on thyroid function, vitamin D supplementation may significantly affect surgical outcomes in Hashimoto's thyroiditis individuals. A study carried out by (Yang et al., 2025) identified deficit in vitamin D as an autonomous predictor of postoperative hypothyroidism and hypocalcemia in individuals undergoing thyroidectomy for Hashimoto's thyroiditis. The study advised preoperative enhancement levels of vitamin D (25(OH)D >30 ng/mL) to mitigate the risk of postoperative problems. The information indicates that vitamin D administration may enhance thyroid function and diminish surgical risks in people with autoimmune thyroid disorders.

For clinicians managing hypothyroid patients in MENA (including Libya), assessing 25(OH)D, correcting deficiency, and then titrating levothyroxine may help optimize TSH control, reduce autoimmune activity, and potentially avoid unnecessarily escalating LT4 doses in vitamin D–deficient individuals (Vivekanand et al., 2025).

The integration of vitamin D evaluation and supplementation in the management of hypothyroidism and autoimmune thyroid conditions has the potential to improve clinical outcomes and reduce disease burden. However, further study is required to develop solid clinical guidelines. Large-scale, randomized controlled studies are required to ascertain the best dose and duration of vitamin D supplementation, as well as to assess the enduring consequences on thyroid functionality and autoimmune markers. Furthermore, investigation is necessary to determine the cost-effectiveness of vitamin D screening and supplementation in various demographics and healthcare settings.

Future Directions and Research Gaps

Even though there is increasing evidence that vitamin D insufficiency causes hypothyroidism, there are still a number of research gaps that must be filled in order to develop firm treatment recommendations. The requirement for extensive, randomized controlled studies (RCTs) to ascertain the causal relationship between hypothyroidism and vitamin D insufficiency is one of the major research gaps. Although an important correlation exists between diminished serum vitamin D levels and an elevated risk of hypothyroidism, observational studies are unable to prove causation. To find out if

vitamin D supplementation can stop hypothyroidism from developing in people who already have a vitamin D deficit, RCTs are required.

A significant research gap exists regarding the determination of the ideal amount and length of vitamin D supplementation for hypothyroidism individuals and autoimmune thyroid disorders diagnosed. Numerous studies indicate that doses ranging from 2000 to 4000 IU/day may be effective; however, the ideal dosage is expected to vary according to factors such as initial vitamin D levels, genetic differences in the VDR gene, and the presence of additional comorbidities. Research on genotype-guided dosing is essential to ascertain the optimal vitamin D supplementation levels for individuals with varying VDR genotypes.

Long-term outcome studies via large-scale randomized controlled trials (RCTs) are crucial for evaluating the sustained impacts the supplementation of vitamin D on autoimmune markers, thyroid function, and disease progression in hypothyroidism and autoimmune thyroid diseases. Most existing trials, nevertheless, are limited to durations of 3-6 months, with variable dosing (1,000-60,000 IU) and inconsistent reductions in antibodies. It is essential for these studies to standardize protocols, monitor outcomes beyond 12 months, and assess the prevention of hypothyroidism progression, levothyroxine dependency, and complications such as thyroid cancer.

Mechanistic study is also required to better understand the molecular routes by which vitamin D impacts thyroid function and autoimmune. While numerous processes have been hypothesized, including regulation of T-helper cell development, modification of B cell activity, and direct effects on thyroid follicular cells, the precise mechanisms are yet unknown. Further investigation is required to elucidate the function of vitamin D in the regulation of the hypothalamic-pituitary-thyroid (HPT) axis, as well as its impact on thyroid hormone production and secretion.

Research on the immunomodulatory impacts of vitamin D on Th17/Tr1 ratios and surgical outcomes in severe hypertension cases is scarce; prospective cohorts in high-prevalence areas such as the Middle East are necessary. The long-term effects on the progression of hypothyroidism, the requirements for levothyroxine, and associated comorbidities, such as celiac disease, necessitate additional investigation.

Lastly, research is required to assess how cost-effective vitamin D screening and supplementation are in various demographics and healthcare environments. The cost-effectiveness of regular screening and supplementation programs needs to be assessed, especially in low-resource settings, even though vitamin D supplementation is reasonably priced. The affordability of screening for vitamin D and supplementation in various populations, such as pregnant women, women of childbearing age, and those with autoimmune illnesses, has to be investigated.

CONCLUSION

The association between insufficient vitamin D levels and the occurrence of hypothyroidism is supported by a rising body of data derived from observational studies, meta-analyses, and interventional trials. The consistent findings of this research demonstrated that insufficient in vitamin D is a significant risk factor for hypothyroidism, particularly autoimmune hypothyroidism like Hashimoto's thyroiditis. The biological basis for this association lies in the immunomodulatory and hormonal mechanisms by which vitamin D influences thyroid function. Vitamin D influences its effects by managing the equilibrium among T-helper cells, encouraging regulatory T cells, inhibiting pro-inflammatory cytokines, and adjusting B cell activity and autoantibody generation.

The ramifications of this association within the clinical context are profound. The incorporation of vitamin D screening and supplementation within the framework of managing hypothyroidism and autoimmune thyroid disorders may enhance clinical outcomes and alleviate the overall disease burden. Routine vitamin D screening in hypothyroidism patients, especially individuals with autoimmune thyroid disorders, should be considered routine clinical practice. If a patient is discovered vitamin D supplementation for those who are vitamin D deficient should be explored as an adjuvant therapy, with doses of 2000-4000 IU/day for at least 3-6 months.

The widespread occurrence of vitamin D deficiency and hypothyroidism in the MENA region, comprising Libya, underscores the importance of implementing targeted screening and intervention initiatives. The clinical environment in Tripoli could benefit from the adoption of vitamin D screening protocols for individuals diagnosed with hypothyroidism and autoimmune thyroid conditions. Furthermore, incorporating vitamin D supplementation into the treatment of hypothyroidism may enhance clinical outcomes and decrease the likelihood of complications.

Even with the encouraging results, there are still a number of research gaps that must be filled in order to develop firm clinical recommendations. To ascertain the ideal dosage and length of vitamin D treatment, in addition to the causal link between vitamin D insufficiency and hypothyroidism, extensive, randomized controlled trials are required. To assess how vitamin D supplementation affects autoimmune markers and thyroid function over time, long-term outcome studies are also required. Lastly, to enhance comprehension of the molecular pathways by which vitamin D influences thyroid function and autoimmune, mechanistic study is required.

In conclusion, vitamin D insufficiency manifests a considerable risk for hypothyroidism, and supplementation of vitamin D may enhance clinical outcomes for patients suffering from hypothyroidism and autoimmune thyroid diseases. The incorporation of vitamin D screening and supplementation into clinical practice may significantly alleviate disease burden and improve the quality of life for those with hypothyroidism. Further investigation is required to formulate definitive clinical guidelines and to improve the efficiency of vitamin D supplementation in hypothyroidism treatment.

ETHICS

There are no ethical issues among the authors regarding the publication of this manuscript.

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الملخص

يُعدّ قصور الغدة الدرقية مرضًا شائعًا في الغدد الصماء، يتميز بنقص في إنتاج هرمونات الغدة الدرقية، وقد أصبح مشكلة صحية خطيرة على مستوى العالم. في الوقت نفسه، يرتبط نقص فيتامين د، وهو نقص غذائي متوطن، بشكل متزايد بمجموعة متنوعة من أمراض المناعة الذاتية واضطرابات الغدد الصماء. يهدف هذا الاستعراض إلى تلخيص الدراسات المنشورة حاليًا حول نقص فيتامين د وقصور الغدة الدرقية، مع التركيز بشكل خاص على الآليات المناعية والأهمية السريرية. أُجري استعراض للدراسات الحديثة (2020-2025)، بما في ذلك الدراسات الرصدية والتحليلات التلوية والتجارب السريرية. تشير النتائج إلى وجود ارتباط ملحوظ بين انخفاض مستويات فيتامين د في الدم وزيادة خطر الإصابة بقصور الغدة الدرقية، وخاصة قصور الغدة الدرقية المناعي الذاتي مثل التهاب الغدة الدرقية لهاشيموتو. من الناحية الآلية، يُمارس فيتامين د تأثيرات مناعية معدلة من خلال تنظيم التوازن بين الخلايا التائية المساعدة، وتعزيز نشاط الخلايا التائية التنظيمية مع تثبيط إنتاج السيتوكينات المُحفزة للالتهاب، وبالتالي التأثير على المناعة الذاتية للغدة الدرقية. أظهرت دراسات سكانية واسعة النطاق، بما في ذلك المسح الوطني لفحص الصحة والتغذية (NHANES)، نسب احتمالية مُعدّلة تتراوح بين 1.6 و1.7 للإصابة بقصور الغدة الدرقية لدى الأفراد الذين يعانون من نقص فيتامين د. وتؤكد التحليلات التلوية هذه النتائج، مشيرةً إلى انخفاض ملحوظ في مستويات فيتامين د في مصل الدم لدى مرضى قصور الغدة الدرقية والتهاب الغدة الدرقية لهاشيموتو مقارنةً بالأفراد الأصحاء.

وقد أظهرت بعض الدراسات فعالية مكملات فيتامين د في خفض مستويات الأجسام المضادة للغدة الدرقية وتعزيز وظائفها، إلا أن الفوائد السريرية لا تزال متفاوتة، ويبدو أنها أكثر فعالية لدى الأفراد ذوي وظائف الغدة الدرقية الطبيعية الذين يعانون من نقص فيتامين د في الأساس. وتخلص هذه المراجعة إلى أن نقص فيتامين د يُعد عامل خطر مهمًا للإصابة بقصور الغدة الدرقية، وتُسلط الضوء على إمكانية استخدام مكملات فيتامين د كعلاج مساعد، لا سيما في المجتمعات التي ينتشر فيها كلا المرضين على نطاق واسع، كما هو الحال في الشرق الأوسط وشمال إفريقيا. ولصياغة إرشادات سريرية قاطعة، يلزم إجراء المزيد من التجارب السريرية العشوائية المضبوطة.

الكلمات المفتاحية: نقص فيتامين د، قصور الغدة الدرقية، تعديل المناعة، مكملات فيتامين د.