Chettinad Health City Medical Journal
Volume 14, Issue 4 - 2025, Pg. No. 43-48
Peer Reviewed & Open Access Journal

Review Article

The interrelation of vitamin D deficiency and thyroid dysfunction among type 2 diabetes mellitus patients-A REVIEW

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DOI: https://doi.org/10.24321/2278.2044.202548

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How to cite this article:
Vijayasamundeeswari, Sayanam R R A. The interrelation of vitamin D deficiency and thyroid dysfunction among type 2 diabetes mellitus patients-A REVIEW. Chettinad Health City Med J. 2025;14(4):43-48.

Date of Submission: 2024-08-29
Date of Acceptance: 2025-08-04

A B S T R A C T

The review highlights the significant interplay between thyroid dysfunction, vitamin D deficiency, and diabetes mellitus, particularly type 2 diabetes (T2DM). Here are the key points discussed:

Prevalence of Conditions: There is a documented increase in the prevalence of thyroid disorders and vitamin D deficiencies among patients with diabetes mellitus. This suggests a common underlying pathology that warrants further investigation.

Impact on Metabolic Control: Untreated thyroid dysfunction and low vitamin D levels (hypovitaminosis D) can impair metabolic control in diabetic patients. This impairment can lead to higher risks of cardiovascular diseases, emphasizing the need for integrated management strategies.

Insulin Resistance: Insulin resistance is a critical link between thyroid dysfunction and diabetes. The review suggests that both conditions can exacerbate each other, complicating the overall metabolic health of affected individuals.

Need for Systematic Testing: Given the clinical implications of the co-occurrence of T2DM and thyroid dysfunction, the review advocates for a more intrinsic approach to thyroid testing in diabetic patients. Consistent monitoring of glycemic control alongside thyroid function and vitamin D status is recommended.

Call for Further Research: The review concludes with a call for more research to better understand the relationships between vitamin D, thyroid dysfunction, and diabetes. This could lead to improved management strategies for patients suffering from these interconnected conditions.

Keywords: Thyroid Dysfunction, Diabetes Mellitus, Vitamin D, Autoimmune Diseases

Introduction

T2DM is distinguished by two primary mechanisms: the impaired secretion of insulin by the β cells of the pancreas and the lack of ability of insulin-sensitive tissues to respond effectively to insulin. This duality leads to insulin resistance and impaired glucose metabolism, contributing to the overall metabolic dysfunction associated with T2DM. Diabetes threatens 422 million people worldwide, according to estimates from the World Health Organization (WHO), with a large percentage of those suffering living in low- and middle-income nations. Specifically, it was estimated that 74.9 million Indians had been diagnosed with diabetes in 2021, and by 2045, that figure is expected to increase to 124.9 million.[1]. Indeed, the WHO reports that around 1.5 million deaths are directly ascribed to diabetes each year, and the prevalence of the disease has been steadily increasing over recent decades. This underscores the urgent need for effective management strategies and preventive measures to address the growing diabetes epidemic. Additionally, numerous studies have established a consistent link between vitamin D deficiency and T2DM. This connection suggests that inadequate levels of vitamin D may play a role in the development and progression of T2DM, potentially influencing insulin resistance and glycemic control. Furthermore, T2DM and thyroid dysfunction are closely related endocrine disorders. Research indicates that thyroid dysfunction can adversely affect glycemic control in diabetic patients, resulting in elevated levels of glycosylated hemoglobin (HbA1c) and contributing to metabolic imbalances[2]. Vitamin D deficiency, hypothyroidism, and diabetes mellitus are predominant issues globally, with a particularly high incidence in India. Understanding this relationship is crucial, as it may provide insights into potential therapeutic strategies and preventive measures for managing these interconnected health conditions. Therefore, the purpose of this study is to investigate the complex link between thyroid function and vitamin D levels in relation to T2DM.

Vitamin D

The "sunshine vitamin," or vitamin D, is essential for numerous body functions. It's necessary to preserve an appropriate balance of calcium and phosphorus. Vitamin D is recognized to be important for bone health, but recent studies have shown its significance in several other physiological processes. It helps to modulate the immune system and reduce the risk of infections and autoimmune diseases by influencing the activity of immune cells[3]. Adequate levels of vitamin D are associated with cognitive function and may help refrain from neurodegenerative disorders. Furthermore, vitamin D is linked to cardiovascular health; insufficiencies may raise the risk of hypertension and heart disease. Additionally, vitamin D may help modulate blood pressure, minimizing the risk of hypertension and related cardiovascular issues. Additionally, it can affect the expression of genes related to cell proliferation, ensuring that cells divide and proliferate in a controlled way. It prevents uncontrolled cell division, proliferation, and apoptosis, which is the controlled death of certain cell types, and is essential to sustaining tissue homeostasis[4].

Thyroid hormone

Thyroid hormone is essential for several physiological processes, including regulating growth, development, and metabolism. It is synthesized and stored in the thyroid gland, released into the bloodstream, and exerts its effects by binding to nuclear receptors to regulate gene transcription. Thyroid-stimulating hormone (TSH) plays a critical role in the regulation of thyroid hormones. It is produced by the pituitary gland, which also triggers the thyroid gland to secrete and release two important hormones: thyroxine (T4) and triiodothyronine (T3). Cellular differentiation and metabolic processes are subsequently impacted by these hormones[5]. The effects of thyroid hormones are arbitrated by nuclear receptors TRalpha and TRbeta, functioning as transcription factors that regulate gene expression across various tissues and organs. Changes in thyroid hormone levels can result in neurological problems and are linked to neuropsychiatric disorders, exhibiting sex-specific variations in neuronal signaling[6]. Grasping the complex mechanisms of thyroid hormone regulation and its effects on different physiological systems is essential for maintaining overall health and managing related disorders.

Vitamin D and Thyroid Hormone

Vitamin D is essential for the proper functioning of numerous organs, including the thyroid gland. Recent studies have highlighted a significant relationship between vitamin D and its role in regulating the production and release of various hormones, as well as the feedback mechanisms of these hormones on the renal production of vitamin D. Moreover, studies have demonstrated that both excessive and insufficient hormone secretion are linked to vitamin D deficiency[7]. It is widely recognized that the biological actions of vitamin D and thyroid hormones are interconnected; however, the exact relationship between vitamin D and thyroid hormone function is complex and multifaceted. Their actions can influence each other, and deficiencies in one can impact the function of the other. Research has indicated that vitamin D deficiency is associated with a heightened risk of thyroid disorders, including autoimmune thyroid diseases and thyroid cancer[8]. The exact mechanisms through which vitamin D influences thyroid function and vice versa are still being explored.

Vitamin D and Thyroid Disorders

Vitamin D is crucial for immune system modulation because of its dynamic effects on a variety of cells. Lack of vitamin

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202548

D has been related in studies to a higher risk of infections and autoimmune diseases[9]. It influences immune responses by acting on immune cells, including B and T lymphocytes, dendritic cells, and macrophages, through direct attachment to the VDR and the activation of related genes[10]. The vitamin D levels of people with autoimmune thyroid disorders (AITDs), including Hashimoto's thyroiditis and Graves' disease, have been found to be lower. This could raise the likelihood of getting these conditions. Jiying Wang et al.'s meta-analysis found that participants with AITDs had a higher likelihood of having a 25(OH)D deficiency, which could suggest a link between vitamin D deficiency and the genesis of autoimmune thyroid disorders.[11]. The presence of vitamin D receptors (VDR) and 1-alpha hydroxylase in thyroid tissue indicates the possibility of local synthesis of active vitamin D within the thyroid gland. Additionally, research on VDR gene polymorphisms suggests a genetic link between vitamin D pathways and autoimmune thyroid diseases[12]. There is evidence linking vitamin D deficiency to higher antibody levels or an increased risk of autoimmune thyroid diseases. Vitamin D affects immune cells by suppressing T-lymphocyte activation and proliferation, influencing antigen-presenting cell differentiation and maturation, and preventing the production of inflammatory cytokines. Studies have demonstrated that vitamin D can lessen the expression of pro-inflammatory cytokines produced by Th17 cells and prevent the differentiation of Th17 cells into pathogenic types, highlighting its potential therapeutic role in autoimmune thyroid diseases[13].

Diabetes mellitus and thyroid disorder

Thyroid disorders and diabetes are indeed prevalent endocrinological issues in medical practice. Untreated thyroid dysfunction can significantly impair metabolic control in diabetic patients. Research has shown that individuals with hypothyroidism often exhibit higher insulin levels, accompanied by lower insulin clearance, which can complicate diabetes management[14]. This interplay highlights the importance of keeping track of thyroid function in patients with diabetes to ensure optimal metabolic control. The prevalence of hypothyroidism in individuals with type 2 diabetes (T2D) varies between 6% and 20% according to epidemiological studies across different ethnic groups[15]. Both subclinical and overt hypothyroidism are the most common forms of thyroid dysfunction observed in T2D patients[16]. Several factors have been recognized that increase the risk of developing hypothyroidism in this population, including female sex, older age, obesity, and positivity for thyroid peroxidase antibodies (TPO Ab)[17]. This underscores the need for regular screening and monitoring of thyroid function in diabetic patients, particularly those with these risk factors. In a study conducted by E. Maratou et al., it was observed that patients with subclinical and overt hypothyroidism exhibited decreased insulin-stimulated glucose transportation in monocytes. This impairment was attributed to the reduced translocation of GLUT-4 glucose transporters to the plasma membrane, which is crucial for glucose uptake[18]. Additionally, research by AL Sayed and Tuzcu A indicated that while there was a significant increase in insulin levels among patients with subclinical hypothyroidism, no corresponding significant change in insulin resistance was noted. This suggests that the relationship between thyroid function and insulin dynamics is complex and may vary depending on the specific thyroid condition present[19,20]. The study by Lekakis et al., highlighted that hypothyroid patients experience impaired flow-mediated endothelial vasodilation, which contributes to the development of insulin resistance[21]. This finding emphasizes the cardiovascular implications of thyroid dysfunction in relation to metabolic health. Furthermore, research by Kim et al., revealed that thyroid hormones and insulin play a synergistic role in maintaining glucose homeostasis at cellular and molecular levels as well[22]. They hypothesized that a reduction in intracellular thyroid hormone levels impairs insulin-stimulated glucose uptake. Consequently, even a mild decrease in thyroid hormones is inversely correlated with insulin resistance, indicating that thyroid hormone levels are crucial for effective insulin action and glucose metabolism. Furthermore, the literature indicates that both subclinical hypothyroidism and hyperthyroidism can lead to elevated blood pressure and cholesterol levels, impair insulin secretion, and compromise both micro- and macrovascular functions. These effects significantly increase the risk of complications such as peripheral neuropathy, peripheral artery disease, and diabetic nephropathy[23]. Additionally, thyrotoxicosis is associated with increased lipid peroxidation, which can contribute to oxidative stress and vascular damage. In contrast, hypothyroidism is linked to a decrease in glucose oxidation, further complicating metabolic control and potentially exacerbating insulin resistance[24]. This emphasizes the critical role of thyroid hormones in maintaining cardiovascular and metabolic health, particularly in individuals with diabetes. Thyroid hormones (TH) arouse catecholamine activity, which leads to lipolysis in adipocytes and an upsurge in circulating free fatty acids (FA). This elevated supply of free fatty acids can counteract the thyroid hormone-mediated intensification of the hepatic long-chain fatty acid oxidative pathway, which plays a role in gluconeogenesis[25]. These interactions underscore the complex relationship between thyroid diseases and T2DM. The findings suggest that early screening and recognition of risk factors for thyroid dysfunction in diabetic patients could help minimize the risk of developing both conditions and their associated medical complications[26]. This accentuates the importance of integrated management strategies for patients with diabetes and thyroid disorders.

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202548

Vitamin D and Thyroid Disfunction in Type 2 Diabetes Mellitus

Vitamin D deficiency has been found to be significantly associated with thyroid dysfunction in people with type 2 diabetes. Research shows that vitamin D levels and the thyroid hormones FT4 and FT3 are strongly positively correlated. On the other hand, there is evidence of a negative correlation between thyroid-stimulating hormone (TSH) and vitamin D levels [27]. This suggests that adequate vitamin D levels may play a crucial role in maintaining thyroid function, particularly in individuals with T2DM. The study conducted by Atul Debbarma et al. supports the concept that there is an inverse relationship between TSH levels and vitamin D levels, as well as between HbA1c levels and vitamin D levels. According to their studies, vitamin D deficiency is significantly more common in hypothyroid diabetics, and the degree of hypothyroidism is associated with the severity of vitamin D deficiency. Additionally, the study found that lower levels of free T3 and T4 were associated with lower vitamin D levels, further reinforcing the intricate interplay between thyroid function and vitamin D status in patients with type II diabetes mellitus[28]. The research conducted by Quan Li & Rui Bi revealed that among 230 participants, 68.26% of postmenopausal women with T2DM exhibited a deficiency in 25-hydroxyvitamin D (25(OH)D). This study also found a higher prevalence of both hyperthyroidism and hypothyroidism, as well as positive thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) in these individuals compared to those with normal 25(OH)D levels. The findings suggest that vitamin D deficiency has been linked to insulin resistance and poor glycemic control in patients with T2DM. Therefore, monitoring 25(OH)D levels could be beneficial in identifying individuals at risk of developing thyroid disorders[29]. This stresses the need for regular assessment of vitamin D status in managing patients with diabetes and potential thyroid dysfunction. Wang et al., conducted a case-control study involving 2,659 Chinese participants, which demonstrated that low serum levels of vitamin D are associated with T2D. The study explained that this association may be attributed to alterations in the concentrations of total LDL cholesterol and high-density HDL. These lipid profile changes can contribute to impaired fasting glucose levels, thereby increasing the risk of developing T2D[30]. This points up the potential role of vitamin D in metabolic health and its influence on diabetes risk factors. Vitamin D supplementation has been shown to have a positive effect on thyroid function in patients with T2DM who also have thyroid disorders. Specifically, it has been found to increase total thyroxine (T4) levels while simultaneously decreasing thyroid-stimulating hormone (TSH) levels. This suggests that addressing vitamin D deficiency through supplementation may help improve thyroid hormone levels and overall thyroid function in this patient population[31]. Additionally, improving blood glucose management has been linked to treating vitamin D insufficiency in patients with T2DM. Glycosylated hemoglobin (HbA1c), a measure of long-term blood glucose management, has been shown to drop in response to vitamin D replacement therapy. This implies that treating vitamin D deficiency may help people with type 2 diabetes control their blood glucose levels.[32]. This finding highlights the potential therapeutic value of vitamin D supplementation in improving metabolic outcomes such as improvement in insulin sensitivity, glycemic control, and overall metabolic health in diabetic patients.

Conclusion

The conclusion supports the routine screening of vitamin D levels and thyroid function tests in patients with diabetes mellitus. This includes testing for thyroid peroxidase antibodies, thyroglobulin antibodies, and vitamin D, which can help to identify thyroid autoimmune disorders and vitamin D deficiencies early. By implementing these screening measures, clinicians can better identify and treat thyroid disorders and vitamin D deficiencies in diabetic patients. This proactive approach may lead to improved metabolic control and reduced risk of complications associated with both diabetes and thyroid dysfunction. Further, there is a clear call for additional studies to enhance our understanding of how thyroid dysfunction and vitamin D deficiency contribute to the onset and progression of diabetes. This knowledge is crucial for developing effective management strategies.

Conflict of Interest: None

Source of Funding: None

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: None

Author's Contribution: V: contributed to the conceptualization and literature review. RRAS: contributed to manuscript drafting and critical revision. Both authors read and approved the final manuscript.

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ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202548