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Review Article

VITAMIN D AS A POTENTIAL MODULATOR OF INFLAMMATION IN TYPE 2 DIABETES: A REVIEW

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ABSTRACT

Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance and impaired insulin secretion. In recent years, vitamin D has emerged as a potential modulator of T2D development and progression, with studies showing a link between vitamin D deficiency and an increased risk of developing the disease. In this review, we aim to provide a comprehensive overview of the current literature on the relationship between Vitamin D, inflammation, and type 2 diabetes. We will highlight the gaps in current knowledge and propose directions for future research to elucidate the role of vitamin D in the development and management of type 2 Diabetes and its underlying mechanisms. In conclusion, Vitamin D has been shown to have a beneficial effect on the regulation of glucose metabolism in the body. Therefore, a holistic approach to preventing and managing Type 2 Diabetes should involve a combination of strategies including regular physical activity, healthy eating habits, stress management, and medical interventions as necessary**.**

Keywords: vitamin D; inflammation; Insulin Resistance; Inflammatory Response; immune system

INTRODUCTION

Type 2 diabetes (T2D) is a prevalent metabolic disorder affecting millions of individuals worldwide. It is characterized by insulin resistance and beta-cell dysfunction, leading to impaired glucose regulation and long-term complications such as cardiovascular disease, neuropathy, and retinopathy. **(1)** In recent years, vitamin D has emerged as a potential modulator of T2D development and progression, with studies showing a link between vitamin D deficiency and an increased risk of developing the disease.**(2)(3)(4)** Initial observations linking vitamin D to T2D in humans came from studies demonstrating seasonal variations in glycemic control in both healthy and diabetic subjects.**(5)** Subsequently, numerous studies have investigated the relationship between vitamin D status and T2D, with evidence supporting the importance of vitamin D in regulating pathways related to T2D development.**(6)(7)**

One potential mechanism through which vitamin D may affect T2D development is by modulating inflammatory response. **(8)** Inflammatory pathways have been shown to interfere with normal metabolism and disrupt proper insulin signaling, ultimately leading to T2D. Theoretically, vitamin D might affect glucose homeostasis by reducing inflammatory response. A few trials have looked at the effects of vitamin D supplementation on inflammatory biomarkers in patients with or at high risk of developing T2D, but the results are conflicting and few. **(9)(10)**

According to the existing clinical and epidemiological data, vitamin D's beneficial benefits on type 2 diabetes are principally associated with its action on insulin secretion and sensitivity, with its influence on inflammation acting as a byproduct.**(11)(12)** For example, some studies have reported improved insulin sensitivity and beta-cell function in individuals supplemented with vitamin D.**(13)(14)**, whereas others have shown no significant effects.**(15)** To establish a more solid connection between vitamin D, inflammation, and T2D, further research is needed on the function of vitamin D in inflammatory processes and its possible effects on T2D.

Given the increasing prevalence of T2D and the potential for vitamin D to modulate its development, it is crucial to understand the underlying mechanisms of action.**(16)** Specifically, future studies are needed to investigate the role of vitamin D on T2D using inflammation as the main outcome. Such studies could help identify individuals at risk of developing T2D and provide insights into potential therapeutic interventions. Additionally, as vitamin D deficiency is prevalent worldwide, investigating its role in T2D development could provide a cost-effective and accessible means of preventing or managing the disease.**(17)**

In this review, we aim to provide a comprehensive overview of the current literature on the relationship between vitamin D, inflammation, and T2D. We will examine the available clinical and epidemiological evidence and discuss the potential mechanisms through which vitamin D may modulate T2D development and progression.**(18)** Furthermore, we will critically evaluate the existing studies investigating the impact of vitamin D supplementation on inflammatory biomarkers in individuals with or at high risk of developing T2D.**(19)(20)** Finally, we will highlight the gaps in current knowledge and propose directions for future research to elucidate the role of vitamin D in T2D and its underlying mechanisms.

Inflammation, Insulin Resistance and Type 2 Diabetes

Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance and impaired insulin secretion. The prevalence of T2D is rapidly increasing worldwide, and it is projected to affect 700 million people by 2045.**(21)** Chronic low-grade inflammation is a common feature of T2D and is closely associated with the development of insulin resistance.**(22)** Inflammation plays a pivotal role in the pathogenesis of T2D by disrupting insulin signaling pathways and promoting the release of pro-inflammatory cytokines.**(23)**

Obesity is characterized by an increase in adipose tissue mass and a persistent low-grade inflammatory state, which makes it a significant risk factor for T2D.**(24)** Numerous studies have linked the development of insulin resistance in peripheral tissues like the liver, skeletal muscle, and adipose tissue to obesity-induced

inflammation.**(25)** Hotamisligil et al. established the first connection between obesity, inflammation, and insulin resistance by showing that obese animals had higher tumor necrosis factor-α (TNF-α) mRNA expression in their adipose tissue and that neutralizing TNF- improved insulin action on glucose uptake.**(26)** Consequently, it has been demonstrated that tissues from obese people have higher levels of a variety of inflammatory cytokines, including interleukin (IL-1, IL-6,) and monocyte chemoattractant protein (MCP-1).**(27)**

By inhibiting insulin receptor substrate (IRS) phosphorylation and activating the phosphatidylinositol 3-kinase (PI3K)-Akt pathway, which is in charge of insulin action on glucose uptake and suppression of gluconeogenesis, the activation of inflammatory pathways interferes with normal metabolism and disrupts proper insulin signaling.**(28)** The insulin receptor signaling cascade is inhibited as a result of the activation of the enzymes c-jun N-terminal kinase (JNK) and inhibitor of B kinase (IKK), which target IRS-1 for serine phosphorylation.**(29)** The fact that additional kinases, including protein kinase C (PKC-Theta), can block IRS-1 through serine phosphorylation suggests that insulin signaling can be blocked by the activation of numerous cellular networks. Pro-inflammatory cytokines can also target cell membrane receptors, contributing to the inflammatory response and escalating insulin resistance. Examples of these cytokines include IL-1 and TNF-α.**(30)** cytokine signaling suppressors (SOCS) 1 and 3, induced by IL-6, lead to ubiquitinylation and degradation of IRS proteins, further impairing insulin signaling.**(31)**

The action of the hormone insulin in peripheral tissues like the liver, skeletal muscle, and adipose tissue is inhibited by metabolic stressors like high blood non-esterified fatty acid (NEFA) levels.**(32)** A systemic factor that affects insulin sensitivity is the hormone adiponectin, which is secreted by adipose tissue. Human monocytes, monocyte-derived macrophages, and dendritic cells are stimulated to produce the anti-inflammatory mediators IL-10 and IL-1 receptor antagonist (IL-1RA) by adiponectin, which also reduces the production of pro-inflammatory cytokines like TNF-α and interferon-g (IFN-g).**(33)** However, adiponectin mRNA expression and protein secretion in adipose tissue are inhibited by certain inflammatory mediators, such as TNF-α and IL-6, which are elevated in obese and insulin-resistant people.**(34)**

Chronic low-grade inflammation plays a pivotal role in the pathogenesis of T2D by disrupting insulin signaling pathways and promoting the release of pro-inflammatory cytokines. **(35)** Obesity-induced inflammation is closely associated with the development of insulin resistance, a key feature of T2D. **(36)**

The Role of Vitamin D in Inflammation

Vitamin D is a fat-soluble vitamin that is essential for the regulation of calcium and phosphorus metabolism and for the growth and maintenance of bones. It can be obtained from the diet, but most of the vitamin D needed by the human body is synthesized in the skin through exposure to sunlight. **(37)** In recent years, evidence has emerged suggesting that vitamin D may also play a role in the modulation of inflammatory response, which could have implications for the prevention and treatment of various chronic diseases.**(38)**

Vitamin D Synthesis and Metabolism

When exposed to sunlight, 7-dehydrocholesterol absorbs ultraviolet B (UVB) photons that enter the skin and cause the production of previtamin D. This vitamin D form is fragile and quickly reorganises to become vitamin D3 (cholecalciferol). Ergocalciferol, also known as

vitamin D2, is the form of vitamin D that naturally occurs in plants and is added to some foods, including fluid milk.**(39)** The liver enzyme vitamin D-25-hydroxylase (25-OHase or CYP27A1) converts both vitamin D forms into 25-hydroxyvitamin D (calcidiol), the primary vitamin D form circulating in plasma and a substrate for the production of the hormonally active metabolite 1,25-dihydroxyvitamin D, 1,25(OH)2D3 (calcitriol). Both vitamin D forms eventually enter the circulation bound to a vitamin D binding protein.**(40)**

The 1,25(OH)2D3 steroid hormone receptor, known as the vitamin D receptor (VDR), is broadly distributed in more than 38 tissues and clearly regulates key genes involved in bone metabolism, oxidative damage, chronic illnesses, and inflammation.**(41)** VDR is constitutively expressed by dendritic cells and macrophages, indicating that vitamin D is crucial in the regulation of the inflammatory response.**(42)** Since both cell types contain the enzymes 25-hydroxylase and 1-hydroxylase, which allow for the formation of 25OHD and 1,25(OH)2D3, respectively, they are able to synthesise 1,25(OH)2D3.**(43)**

Inflammatory Response

TNF-α is one of the most significant cytokines produced by macrophages, which are cells with a high capacity for cytokine synthesis in general.**(44)** The NF-κB-dependent trans-criptional activation, a key regulator of immunological, inflammatory, and stress responses, is mostly responsible for the transcriptional activation of the TNF- α gene in macrophages.**(45)** 1,25(OH)2D3 increases mRNA stability and decreases IkB-phosphorylation in order to up-regulate the inhibitor of NF-κB (IB-) in LPS-stimulated murine macrophages.**(46)** A decrease in activity is brought on by a decrease in NF-κB's nuclear translocation as IB- levels rise.**(47)** It should be mentioned that 1,25(OH)2D3 has anti-inflammatory effect in macrophages given the crucial involvement of NF-B as a transcription factor of inflammatory mediators.**(48)**

Additionally, 1,25(OH)2D3 inhibits TLR2 and TLR4 protein and mRNA expression in human monocytes in a time- and dose-dependent manner. Immunological modulation is critical for preventing autoimmune disorders, allergies, and infections. **(49)** Incubating isolated monocytes with 1,25(OH)2D3 attenuates this immunological regulation.**(50)**

As a result of its effects on both the innate and adaptive immune systems, vitamin D is an essential component in the control of the immune system.**(51)** Although vitamin D's effects on immunity and inflammation are complicated, it is evident that many different cell types and tissues are affected by its anti-inflammatory properties.**(52)** Numerous health issues, such as an increased risk of infections, autoimmune disorders, and particular types of cancer, have been related to vitamin D deficiency.**(53)** Therefore, it is important to maintain adequate levels of vitamin D in the body, either through diet or supplementation, in order to support a healthy immune system and overall health. **(54)**

Vitamin D and immune system

Vitamin D plays a crucial role in the modulation of immune and inflammatory responses.**(55)** The metabolism of vitamin D in immune cells is an essential process that enables the synthesis of 1,25(OH)2D3, which has anti-inflammatory effects.(56) Macrophages, dendritic cells, and lymphocytes express Vitamin D Receptor (VDR), indicating an important role for vitamin D in the modulation of immune responses.**(57)** The expression of 1α-hydroxylase, an enzyme necessary for the production of 1,25(OH)2D3, is

regulated differently in macrophages and dendritic cells than in the kidneys.**(58)** This is relevant because high levels of 1,25(OH)2D3 and calcium in macrophages can lead to hypercalcemia, which does not happen in kidney cells.**(59)** The balance between Th1 and Th2 responses can determine the outcome of different immunologically mediated clinical syndromes, including infectious, autoimmune, and allergic diseases.**(60)** It has been demonstrated that IL-12 favors the differentiation of naive CD4þ Th lymphocytes to Th1, whereas the presence of IL-4 induces the Th2 phenotype**.(61)** The modulatory effect of vitamin D on the Th1 and Th2 responses is related to the binding of VDR/retinoid X receptor to a silencer region in the promoter region of IFN-g gene**.(62)** Besides, the upregulation of GATA3 transcription factor caused by 1,25(OH)2D3 favors the development of Th2 response. **(63)**

Immune cells, particularly antigen-presenting cells like macrophages and dendritic cells, can synthesize 1,25(OH)2D3 because they express the enzymes 25-hydroxylase and 1a-hydroxylase, necessary for the production of 25(OH)D3 and 1,25(OH)2D3, respectively.**(64)** Conversely, lymphocytes can only express 1a-hydroxylase and are only capable of converting 25(OH)D3 into 1,25(OH)2D3.**(65)** This process is crucial because 1,25(OH)2D3 binds to the VDR, leading to the repression of the expression of proinflammatory cytokines like interleukin-2 (IL-2) and interferon-gamma (IFN-g), and an increase in the production of anti-inflammatory cytokines like IL-4, IL-5, and IL-10. **(66)**

It has also been reported that 1,25(OH)2D3 inhibits activation-induced cell death, a mechanism for negative selection of immature T cells in the thymus and for maintenance of peripheral tolerance.**(67)** Fas and its ligand (FasL/CD95L) regulate this process, and 1,25(OH)2D3 inhibits activation-induced cell death, fasL mRNA expression, and that 1,25(OH)2D3-activated VDR represses fasL promoter activity by a mechanism dependent on the presence of a functional VDR DNA-binding domain and ligand.**(68)**

It is important to consider that vitamin D deficiency is highly prevalent worldwide, and it has been linked to various immunologically mediated disorders.**(69)** For instance, a recent study suggests that vitamin D deficiency may be a risk factor for the development of COVID-19.**(70)** Although the relationship between vitamin D and COVID-19 is not yet fully understood, some studies have suggested that vitamin D supplementation may have a protective effect against COVID-19 infection.**(71)**

Vitamin D plays a critical role in the modulation of immune and inflammatory responses. The metabolism of vitamin D in immune cells is necessary for the synthesis of 1,25(OH)2D.

The Role of Vitamin D in Type 2 Diabetes: Evidence from Human Studies

Type 2 diabetes is a complex metabolic disorder characterized by impaired pancreatic β-cell function, insulin resistance, and inflammation. **(72,73).** Although the underlying pathogenesis of type 2 diabetes is still not fully understood, it is believed that both genetic and environmental factors play a role in its development. Recent evidence has highlighted the potential role of vitamin D in the development and management of type 2 diabetes.**(74)** In this article, we will discuss the evidence from human studies linking vitamin D and type 2 diabetes.

Vitamin D is a fat-soluble vitamin that is primarily synthesized in the skin upon exposure to sunlight. It can also be obtained through diet and supplements. Vitamin D has a wide range of biological functions, including the regulation of

calcium and phosphorus metabolism, modulation of the immune system, and control of cell proliferation and differentiation. **(75)**

The relationship between type 2 diabetes and vitamin D is complex and multifactorial. Multiple studies suggest that vitamin D could play a part in the development and treatment of type 2 diabetics. Initial observations that vitamin D is linked to type 2 diabetes were made by studies which showed seasonal variations in glycemic levels of diabetic and healthy subjects. **(76)** Several recent human studies have linked vitamin D levels with the development of type 2 diabetes.

The Nurses' Health Study studied 83,779 women over a period of 20 years and found that the higher the vitamin D intake, the lower the risk of type 2 diabetes. **(77)** A meta-analysis of data pooled from two cohort studies involving 8,627 people aged 40-79 found that the higher the serum 25OHD level (a biomarker of vitamin D status), the lower the risk of type 2 diabetes.**(78)**

A study that followed 4,097 people for 17 years found that higher serum 25OHD levels were associated with a lower risk of type 2 diabetes by 30%. After statistical adjustments were made for type 2 risk factors, such as the body mass index (BMI), the association between type 2 and vitamin D was lessened in this study.**(79)** A cohort study of 4157 non-smokers followed for 11 years and 1,962 smoking smokers found that the baseline serum 25OHD level was negatively associated with type 2.**(80)**

Other human studies have also reported similar results. In a nested study of 608 patients and 559 controls, the higher versus lower serum 25OHD was associated with 48% less risk of type 2 diabetes. **(81)** In a cross-sectional analysis of 2,465 Caucasian subjects, serum 25OHD >=80 nmol/L and =37 nmol/L were associated with a 50% reduced risk of type 2 diabetes. **(82)** A systematic review of seven observational cohorts involving 238,424 people aged 30-75 found that vitamin-D intake of > 500 UI versus 200 UI was linked to a 13% reduced risk of type 2 diabetes. The serum 25OHD (>25ng/mL as opposed to 14ng/mL), was associated with 43% less risk of type 2 diabetes. **(83)**

Further, epidemiological evidence suggests that vitamin D supplements may be an inexpensive and effective way to not only reduce the risk of type 2 diabetes but also improve the glycemic levels in patients with this condition.**(84)** Vitamin D supplementation is recommended for subjects with high risk of developing type 2 diabetes, and a serum 25OHD baseline level of 26.50 nmol/L. **(85)**

The meta-analysis also found that daily vitamin D supplements of 1000 to 4000 IU led to a significant decrease in HbA1c by 0.37% among diabetic patients. **(86)** It is important to remember that excessive vitamin D consumption can cause toxicity and hypercalcemia. Hypercalciuria may also result. It is therefore recommended that serum 25OHD and calcium levels be monitored during vitamin D supplementation, and excessive doses avoided. **(87)** There is some evidence that suggests a link between vitamin D and the development and management of type 2 diabetes. **(84)** Vitamin D may play a role, although the exact mechanism remains unclear, in insulin release and synthesis, insulin sensitivity and inflammation. Studies have shown that low vitamin D levels are associated with an increased risk for type 2 diabetes. Vitamin D supplementation can also improve glycemic management and reduce the risk for type 2 diabetes among high-risk groups. **(84, 85**) It is important to remember that further research is required to determine the optimal dosages and

duration of supplementation with vitamin D for managing and preventing type 2 diabetes.

CONCLUSION

In conclusion, Vitamin D has been shown to have a beneficial effect on the regulation of glucose metabolism and insulin secretion in the body. Research suggests that maintaining adequate levels of Vitamin D in the body may reduce the risk of developing Type 2 Diabetes. However, the precise mechanism through which Vitamin D exerts its effect on glucose metabolism is still being studied.

Inflammation has also been implicated in the development of Type 2 Diabetes, as chronic inflammation can interfere with the body's ability to regulate glucose levels. Lifestyle factors such as diet, exercise, and stress management can all play a role in reducing chronic inflammation in the body.

It is important to note that while both Vitamin D and inflammation have been linked to Type 2 Diabetes, they are not the only factors at play in the development of the disease. Genetic predisposition, age, and obesity are also significant risk factors for Type 2 Diabetes. Therefore, a holistic approach to preventing and managing Type 2 Diabetes should involve a combination of strategies including regular physical activity, healthy eating habits, stress management, and medical interventions as necessary.

Overall, these articles highlight the importance of maintaining a healthy lifestyle and monitoring one's Vitamin D levels in reducing the risk of developing Type 2 Diabetes. By adopting healthy habits and making informed choices about diet and exercise, individuals can take control of their health and reduce their risk of developing chronic diseases such as Type 2 Diabetes.

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