Advances in Modern Biomedicine

https://amb.cultechpub.com/amb

Cultech Publishing

Review

Evaluation of the Relationship Between Vitamin D and Inflammation in Type 2 Diabetes and Diabetic Complications

Tuba Taslamacioglu Duman*

Department of Internal Medicine, Bolu Abant İzzet Baysal University Faculty of Medicine, Bolu, Turkiye

*Corresponding author: Tuba Taslamacioglu Duman, doktortuuba@gmail.com

Abstract

Type 2 diabetes mellitus (T2DM) and its microvascular complications are characterized by chronic inflammation, which arises as a consequence of persistent hyperglycemia and insulin resistance. In obese patients with T2DM, abdominal adiposity further contributes to metabolic imbalance and an increased inflammatory burden. During the inflammatory process in adipose tissue, proinflammatory cytokine levels rise, while anti-inflammatory cytokines decrease. Vitamin D has been increasingly recognized for its role in modulating inflammation, a key factor in the progression of T2DM and its associated complications. This review examines the relationship between vitamin D status and inflammatory markers in individuals with T2DM, highlighting the potential mechanisms through which vitamin D influences immune responses and metabolic pathways. Recent clinical and experimental studies investigating the impact of vitamin D deficiency on chronic inflammation (such as via tumor necrosis factor alpha, interleukins, and C-reactive protein), insulin resistance, and the development of diabetic complications including cardiovascular disease, nephropathy, and neuropathy are discussed. Furthermore, the review elaborates on the potential benefits of vitamin D supplementation in managing inflammation and mitigating disease progression. Although existing evidence suggests a strong link between vitamin D and inflammatory processes in T2DM, further well-designed clinical trials are needed to establish causality and determine optimal supplementation strategies.

Keywords

Inflammation, Vitamin D, Type 2 diabetes mellitus, Diabetic complications

Article History

Received: 30 July 2025
Revised: 24 October 2025
Accepted: 20 November 2025
Available Online: 26 November 2025

Copyright

© 2025 by the authors. This article is published by the Cultech Publishing Sdn. Bhd. under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0): https://creativecommons.org/licenses/by/4.0

1. Introduction

Type 2 diabetes mellitus (T2DM) is a systemic disease characterized by chronic inflammation. In T2DM and metabolic syndrome, systemic inflammation occurs at the tissue level, particularly in the pancreas, liver, muscles, and adipose tissue [1]. The production of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1 (IL-1), as a result of macrophage infiltration is the beginning of the basic mechanism [2]. The contribution of this chronic inflammatory process to the micro and macrovascular diabetic complications seen in diabetes is quite high.

Vitamin D is known as an important immunomodulatory hormone, in addition to supporting the skeletal system by regulating calcium and phosphate metabolism [3]. Low serum vitamin D levels have been associated in the literature with multiple immune-related diseases, including autoimmune disorders and infectious diseases [4]. In a study evaluating the relationship between vitamin D levels and diabetes regulation in patients with T2DM, a negative correlation was shown between vitamin D and glycated hemoglobin (HbA1c) [5]. Vitamin D also plays an important role in the development of diabetic complications such as diabetic nephropathy. Several animal studies have observed lower vitamin D levels in the diabetic kidney disease group compared to the control group [6-12].

While many studies explored vitamin D in diabetes, the specific link to inflammation remains less clearly synthesized. In this review, we aimed to evaluate the relatıonship between vitamin D and T2DM and its complications in the context of inflammation.

2. T2DM and Inflammation

T2DM is a common metabolic disease characterized by chronic low-grade inflammation and immune system activation. In diabetes and metabolic syndrome, macrophage infiltration contributes to tissue-level inflammation, and pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1, released from these cells, play a key role in pathophysiology. These cytokines also function through autocrine and paracrine signaling to contribute to insulin resistance by disrupting insulin signaling pathways in peripheral tissues, such as skeletal muscle, adipose tissue, and the liver [2,13].

Initially, it was determined that the release and production of the pro-inflammatory cytokine TNF-α in adipose tissue increased in obese individuals, contributing to insulin resistance. Later studies also demonstrated an upregulation of genes regulating inflammatory factors [14].

In obesity, macrophage infiltration into adipose tissue is closely associated with the degree of obesity, systemic inflammation, insulin levels, and, in this context, the development of diabetes and metabolic syndrome [15,16]. Although macrophage-derived pro-inflammatory cytokines in adipose tissue contribute to inflammation, enlarged fat cells themselves are also known to produce pro-inflammatory cytokines and chemokines [17]. Studies have shown that weight loss increases insulin sensitivity and reduces the expression of pro-inflammatory genes [15-17].

In T2DM, inflamed adipose tissue secretes excessive inflammatory cytokines such as TNF-α and IL-6, which stimulate C-reactive protein (CRP) production in the liver and trigger chronic inflammation [18]. The ‘inflammation hypothesis’ suggests that obesity promotes the production of inflammatory molecules by facilitating macrophage migration into adipose tissue, leading to pathological changes in insulin-sensitive tissues and β-cells, ultimately contributing to chronic inflammation [19].

Chronic low-grade systemic inflammation associated with diabetes impairs pancreatic islet cell function and disrupts insulin secretion. During the initial stages of β-cell dysfunction, inflammatory cytokines interfere with intracellular calcium influx and storage, both of which are essential for proper insulin release [20,21].

During the chronic phase, inflammatory signaling via the nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways induces mitochondrial stress and promotes the production of reactive oxygen species (ROS), ultimately resulting in β-cell apoptosis [22,23].

TNF-α, IL-6, and CRP are pro-inflammatory cytokines secreted from adipose tissue that contribute to low-grade inflammation in diabetes, obesity, and metabolic syndrome. They also play a role in atherogenesis [24,25]. CRP, in particular, is an important marker of vascular inflammation and a predictor of atherosclerosis [26-28]. TNF-α activates the transcription factor NF-κB, which regulates inflammatory changes in vascular tissue [29,30]. Additionally, IL-6 increases TNF-α levels [31].

In mouse models of obesity, a higher number of cytotoxic CD8+ effector cells is believed to trigger the recruitment and activation of adipose tissue macrophages, hence, promoting pro-inflammatory cascades linked to insulin resistance [32-34]. Obesity disturbs the balance between pro-inflammatory T helper 1 and 17 cells and anti-inflammatory T helper 2 and regulatory T lymphocytes (subsets of CD4+ cells), resulting in increased cytokine secretion by adipose tissue macrophages [32,34]. Importantly, the number of anti-inflammatory regulatory T lymphocytes is reduced in the adipose tissue of both obese mice and humans [32,34,35], with an even more pronounced decline observed in obese individuals with metabolic syndrome [36].

Regulatory T lymphocytes produce the anti-inflammatory cytokine IL-10, which inhibits macrophage migration and promotes the differentiation of M2 macrophages [35,37]. Consequently, these anti-inflammatory T cells may help suppress adipose tissue inflammation and contribute to protection against obesity-related, insulin resistance–induced inflammation [35,36]. In summary, current evidence in the literature supports the involvement of inflammation, and the potential modulatory role of vitamin D, in the pathogenesis of T2DM and its chronic complications.

3. Diabetic Complications and Inflammation

T2DM is associated with both microvascular and macrovascular complications. Microvascular complications, particularly in patients with poor blood glucose control, develop over time due to chronic hyperglycemia. Inflammatory processes in diabetes also contribute to the pathogenesis of these complications. Pro-inflammatory cytokines, which mediate chronic inflammation in T2DM, play a key role in vascular complications and promote atherosclerosis.

Diabetic nephropathy, a frequent complication of T2DM, is a progressive disorder that significantly contributes to morbidity and mortality due to end-stage renal disease and the subsequent need for hemodialysis. Macrophage infiltration plays a central role in the pathogenesis of both T2DM and diabetic nephropathy. Key factors contributing to the development of diabetic nephropathy include chronic hyperglycemia, oxidative stress, and activation of the renin-angiotensin-aldosterone system. Furthermore, the progression of nephropathy is exacerbated by adhesion molecules, chemokines, cytokines, immune cells, and inflammatory intracellular signaling pathways [38-40].

Research on the pathogenesis of diabetic nephropathy has shown elevated macrophage infiltration and increased expression of leukocyte adhesion molecules in the kidneys of both diabetic patients and experimental animal models [41-45]. Inflammatory cells, such as leukocytes, monocytes, and macrophages, are also implicated in the development of diabetic nephropathy [41-45]. Moreover, circulating pro-inflammatory cytokines contribute to the progression of diabetic complications [44-49].

Inflammation also contributes to the pathogenesis of diabetic retinopathy. Chronic low-grade inflammation is commonly observed in both animal models and diabetic patients at various stages of the disease [50]. Leukocytosis is an important inflammatory marker in the early stages of diabetic retinopathy and is associated with adhesion molecule-mediated leukocyte-endothelial adhesion [51,52]. Overall, chronic inflammation in diabetes triggers an inflammatory cell response, further impairing capillary function and contributing to the development of diabetic retinopathy.

The pathogenesis of diabetic neuropathy is multifaceted, involving several proposed mechanisms. Recent findings from studies using animal models of both type 1 and T2DM suggest that low-grade intraneural inflammation is a contributing feature of diabetic neuropathy [53].

When evaluating the chronic complications of diabetes, it becomes evident that their pathogenesis involves a slow-progressing, chronic inflammatory process driven by hyperglycemia.

4. Vitamin D and Inflammation

Vitamin D, which is essential for bone metabolism, is a fat-soluble prohormone with endocrine, paracrine and autocrine functions [54].

Vitamin D exists in two forms: ergocalciferol (vitamin D_2), obtained from dietary sources, and cholecalciferol (vitamin D_3), synthesized in the skin upon exposure to ultraviolet (UV) light [55]. Once in the bloodstream, both forms are converted in the liver by the enzyme vitamin D-25-hydroxylase into 25-hydroxyvitamin D [25(OH)D]. This metabolite is then transformed into the biologically active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], primarily in the kidneys by the enzyme 25-hydroxyvitamin D-1α-hydroxylase [56-58]. The active form of vitamin D binds to the vitamin D receptor (VDR) located in the cytoplasm of target cells, promoting its heterodimerization with the retinoid X receptor (RXR) to form a VDR-RXR complex [59]. Notably, VDR is expressed not only in the kidneys but also in various other tissues, including the pancreas.

Vitamin D influences immune function both directly and indirectly by regulating the proliferation, differentiation, and activity of immune cells. Macrophages and lymphocytes express the VDR, rendering them responsive to its effects. Vitamin D suppresses the production of chemokines and pro-inflammatory cytokines by macrophages. A deficiency in vitamin D hampers macrophage maturation and reduces the synthesis of key antimicrobial components such as macrophage-specific membrane antigens, lysosomal acid phosphatase, and hydrogen peroxide. Conversely, vitamin D enhances the expression of membrane markers, enzymes, and ROS, thereby promoting chemotaxis and phagocytosis [60]. Furthermore, activated macrophages can synthesize $1,25(OH)_2D_3$ in response to interferon-gamma and toll-like receptor activation.

In recent years, vitamin D has become a very popular research topic, and the relationship between vitamin D and inflammation is also widely covered in the literature. When evaluated, vitamin D causes inflammation by causing both an increase in proinflammatory cells and a decrease in anti-inflammatory cells. It is also evident in the literature that vitamin D has an effect on immune cells. It is thought that the anti-inflammatory effect of vitamin D, one of the extraskeletal effects, may also be effective in diseases such as diabetes that progress with chronic inflammation.

Vitamin D is obtained from skin synthesis (cholecalciferol) and diet, then sequentially hydroxylated to 25-hydroxyvitamin D (25OHD) in the liver and to the active form 1,25-dihydroxyvitamin D (1,25[OH]$_2$D) by 1α-hydroxylase (CYP27B1), classically in the kidney but also in many extra-renal tissues including immune cells. Local (intracrine/paracrine) production of 1,25[OH]$_2$D by immune cells enables autocrine regulation of immune responses that is distinct from endocrine control of mineral metabolism. Regulatory steps include control of hepatic 25-hydroxylases (i.e., CYP2R1), tissue-specific expression of CYP27B1, and catabolism by CYP24A1; together these determine local ligand availability and thus tissue-specific VDR signaling [61, 62]. Many immune cell types express the VDR and the enzymes required for local activation of vitamin D, making them direct targets of 1,25[OH]$_2$D. Binding of 1,25[OH]$_2$D to VDR modulates transcription of a wide array of immune genes through VDREs (vitamin D response elements) and also alters chromatin accessibility at immune loci. Functionally, VDR signalling in antigen-presenting cells suppresses dendritic cell maturation and antigen presentation (reduced IL-12, costimulatory molecules), shifts T-cell differentiation away from pro-inflammatory Th1/Th17 phenotypes toward regulatory/Treg and Th2 profiles, and limits B-cell proliferation and plasma cell differentiation in many contexts. These direct effects manifest as reduced production of proinflammatory cytokines (i.e., IL-12, IFN-γ, TNF-α) and increased anti-inflammatory mediators in vitro and in vivo [63,64]. Beyond direct transcriptional control, VDR activation modulates central intracellular signaling networks that shape immune responses. A well-characterized mechanism is inhibition of NF-κB signaling: VDR can interfere with NF-κB activation, thereby reducing NF-κB nuclear translocation and downstream transcription of proinflammatory genes (IL-6, IL-8, TNF-α, IL-12). Vitamin D also upregulates negative regulators of MAPK signaling (i.e., MKP-1) and influences other pathways such as MAPK and signal transducer and activator of transcription (STATs), contributing to lowered cytokine production and attenuated inflammatory amplification loops. These pathway-level effects help explain how modest changes in ligand availability can produce broad shifts in immune tone and susceptibility to hyperinflammation [65,66]. Because immune cells both produce and respond to 1,25[OH]$_2$D, vitamin D signaling acts at two levels. Cell-intrinsic VDR-mediated transcriptional control that directly alters cytokine and surface-molecule programs, and modulation of intracellular signaling hubs (i.e., NF-κB, MAPK) that amplify or silence inflammatory networks. The combined action, restricted local activation plus VDR-dependent repression of pro-inflammatory pathways, causes a plausible molecular basis for vitamin D's reported effects on infection control, autoimmunity modulation, and dampening of cytokine storms [61].

5. Vitamin D and T2DM

Vitamin D levels are closely related with inflammation and T2DM is characterized with chronic inflammation. Indeed, numerous studies in the literature have explored the link between vitamin D deficiency and various health conditions, including autoimmune diseases, cancer, diabetes mellitus, metabolic syndrome, cardiovascular disease, and hypertension [67-74].

Preclinical studies suggest that vitamin D plays a regulatory role in insulin secretion, beta cell survival, and calcium influx into pancreatic beta cells. Several studies have demonstrated that vitamin D deficiency impairs glucose-stimulated insulin secretion in rat beta cells [75-79], whereas vitamin D supplementation appears to restore this glucose-dependent insulin response [75,78-82].

The enzyme 25(OH)D-1α-hydroxylase also activates vitamin D within pancreatic beta cells, enabling a significant paracrine effect of circulating 25-hydroxyvitamin D [83]. Additionally, vitamin D helps regulate extracellular calcium levels in these beta cells [84]. Since insulin secretion is a calcium-dependent process [85], alterations in calcium flux directly influence insulin release [86-88]. Vitamin D modulates the activity of calbindin, a cytosolic calcium-binding protein present in pancreatic beta cells [89,90], thereby acting as a key regulator of depolarization-induced insulin secretion through the control of intracellular calcium levels [91].

Vitamin D may also directly influence beta cell function, an effect that seems to be mediated through the binding of its circulating active form to the VDR expressed in pancreatic beta cells [89]. For instance, mice deficient in a functional VDR exhibit impaired insulin secretion in response to a glucose challenge, which is linked to reduced insulin production by the beta cells [92].

Although vitamin D plays a regulatory role at several important points when looking at the relationship between vitamin D and diabetes, the development of T2DM has not been prevented despite vitamin D supplementation in the literature. This may be due to a more complex infrastructure in the pathogenesis of T2DM. Metabolically, the effect of insulin resistance not only in the pancreas but also in the liver, muscle and fat tissue increases inflammation. It is clear that vitamin D reduces inflammation, but in the literature on diabetes, there are positive results as well as results that show no effect. What we know for sure is that there are no negative results with vitamin D.

Vitamin D may enhance insulin sensitivity in T2DM through its immunomodulatory effects on systemic inflammation. It can protect beta cells from cytokine-induced apoptosis by directly regulating cytokine expression and activity [93-96]. This anti-inflammatory action of vitamin D may involve the downregulation of NF-κB, a key transcription factor responsible for TNF-α and other proinflammatory molecules. Additionally, vitamin D may exert protective effects by inhibiting cytokine-induced Fas expression, thereby preventing beta cell apoptosis and damage [97].

In addition, other ways to reduce systemic inflammation caused by T2DM and prevent beta cell destruction through vitamin D are; blockade of dendritic cell differentiation, inhibition of lymphocyte proliferation, inhibition of foam cell

formation and inhibition of cholesterol uptake by macrophages and enhancement of regulatory T-lymphocyte development [96, 98].

Much of the early evidence linking low circulating 25-hydroxyvitamin D (25[OH]D) to higher risk of T2DM and to worse chronic complications comes from cross-sectional studies, case–control studies, and prospective cohort studies. These range from small clinic series and hospital-based case/control datasets to large prospective cohorts and pooled meta-analyses involving thousands of participants. For example, pooled analyses and meta-analyses have combined data from many cohorts and found inverse associations between 25(OH)D and incident T2DM [99]. The randomized controlled trials (RCTs) evidence base is smaller and heterogeneous. The largest prevention trial to date (the D2d trial) randomized 2423 adults with prediabetes to vitamin D_3 4,000 IU/day versus placebo and was event-driven; it reported no statistically significant reduction in diabetes incidence in the overall trial population [100]. Smaller RCTs and many single-center supplementation trials have sample sizes from a few dozen to several hundred and have used highly variable doses, durations, and endpoints (i.e., fasting plasma glucose, HbA1c, insülin resistance, albuminuria) [101]. Several recent meta-analyses pool either observational studies (for risk/association questions) or RCTs (for supplementation effects). These syntheses often report modest overall effects or subgroup effects, such as benefit in baseline-deficient patients, but they also highlight between-study heterogeneity and study quality issues [102,103].

Obesity/adiposity is a major confounder in those studies. Adipose tissue both stores vitamin D (lowering circulating 25[OH]D) and is causally linked to insulin resistance and progression to T2DM. Many observational studies adjust for body mass index (BMI) but residual confounding by central adiposity, body composition, or adiposity-related metabolic traits is common. Behavioral and environmental confounders include physical activity, outdoor time / sunlight exposure, diet, socioeconomic status, and comorbidities and they correlate with both vitamin D status and diabetes risk or complications and are inconsistently measured or adjusted for across studies. Failure to fully account for these factors can create spurious associations or exaggerate true effects. An observed association between low vitamin D and worse glycemic control may partly reflect reverse causation (sick or less active patients go outdoors less and thus have lower vitamin D), not a protective effect of vitamin D per se. These issues are repeatedly emphasized in major syntheses of the literature [99,100]. Many cohort and case–control studies relied on one serum 25(OH)D measurement. Because vitamin D levels vary with season, recent sun exposure, and illness, a single measure is a noisy proxy for long-term exposure and increases potential misclassification bias. RCTs that monitor intratrial vitamin D exposure show that achieving and maintaining higher intratrial levels may be more predictive of outcome than assignment alone [104].

RCTs on vitamin D differ widely. some enrolled unselected participants (not deficient), others enrolled deficient or high-risk groups; doses range from low (i.e., 800–2000 IU/day) to high (4000 IU/day or intermittent large boluses); durations often < 2–3 years, sometimes too brief to change long-term endpoints such as diabetic nephropathy or retinopathy. The D2d trial was large but enrolled people with prediabetes regardless of baseline vitamin D; subgroup and intratrial exposure analyses suggested benefit in those who achieved higher vitamin D levels, illustrating how baseline status and achieved exposure matter [100].This heterogeneity makes pooling results difficult and explains inconsistent findings across meta-analyses [104].Many supplementation trials use intermediate surrogate outcomes including fasting glucose and HOMA-IR, rather than hard clinical endpoints such as new-onset diabetes, progression to end stage renal disease (ESRD) and vision-threatening retinopathy. Surrogate endpoints can overestimate biological effects and may not translate into patient-relevant improvements in chronic complications. Where hard endpoints are used, trials are often underpowered or too short [102].

Accumulated data in literature confirms the association between serum vitamin D level and T2DM. Diabetic nephropathy progression is driven by glomerular and tubulointerstitial inflammation: activation of NF-κB, upregulation of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines (MCP-1), and profibrotic mediators including tumor growth factor beta (TGF-β). ROS generation, NLRP3 inflammasome activation, macrophage infiltration and RAAS upregulation (local angiotensinogen/AGT) amplify injury to podocytes, endothelium and tubular cells [7,105]. Vitamin D inhibits NF-κB and inflammasome signaling. $1,25(OH)_2D$ (active vitamin D) has been shown to block NF-κB activation in renal cells, reducing expression of AGT and proinflammatory cytokines; it also suppresses NLRP3 inflammasome activation in experimental models, lowering IL-1β release and downstream inflammation [106, 107]. VDR activation in podocytes reduces high-glucose–induced apoptosis by inhibiting p38/ERK pathways and downstream pro-apoptotic cascades, helping maintain glomerular filtration barrier integrity [108]. Vitamin D skews macrophages toward anti-inflammatory phenotypes, increases IL-10 production, and curtails dendritic-cell maturation, actions that limit renal immune activation [107]. Vitamin D suppresses intrarenal RAAS components via NF-κB inhibition, which reduces hemodynamic and profibrotic signaling contributing to DN [106]. Multiple preclinical studies and smaller clinical trials show reduced proteinuria and inflammatory indices after vitamin D or VDR-agonist treatment. Meta-analyses report decreased albuminuria but inconsistent effects on estimated glomerular filtration rate (eGFR). Heterogeneity in dose, baseline vitamin D status and trial length limit firm conclusions. Mendelian/randomization data are mixed [6,109].

In animal and cell models, vitamin D reduced retinal ROS, inhibited TXNIP/NLRP3 inflammasome activation, and decreased retinal cell apoptosis, effects that protect BRB integrity [110]. Vitamin D and analogues downregulate vascular endothelial growth factor (VEGF) expression in retinal cells and attenuate pathological neovascularization in experimental models, linking VDR signaling to suppression of pro-angiogenic inflammation [111]. Epidemiologic

studies associate low vitamin D with higher prevalence/severity of diabetic retinopathy (DR), and animal/cell studies show mechanistic plausibility. Clinical intervention data are scant and inconsistent; some small human cohorts suggest correlations between baseline vitamin D and response to ocular therapies, but randomized data demonstrating prevention or progression slowing are lacking [111,112].

Vitamin D reduces NF-κB signaling and downstream cytokine production in neural and glial cells, lowering macrophage recruitment and inflammation in peripheral nerves. It also supports antioxidant defenses that limit ROS-mediated axonal injury [113]. Experimental data indicate vitamin D and its analogs can promote Schwann cell survival/differentiation and upregulate neurotrophic factors, which could preserve axonal integrity and support regeneration. Animal models show recovery of nerve conduction and reduced neuropathic pain behaviors after vitamin D or VDR agonist treatment [114]. Observational studies link low 25(OH)D to higher prevalence and severity of painful diabetic polyneuropathy. Small interventional trials and case series report symptomatic improvement in some patients after supplementation, but high-quality RCT evidence is limited. Heterogeneity in outcome measures, doses and follow-up durations complicate interpretation. Mechanistic human data on nerve tissue VDR expression and intraneural vitamin D metabolism remain sparse [113,115]. Figure 1 shows low serum vitamin D activates inflammatory mechanisms and trigger changes that cause microvascular complications.

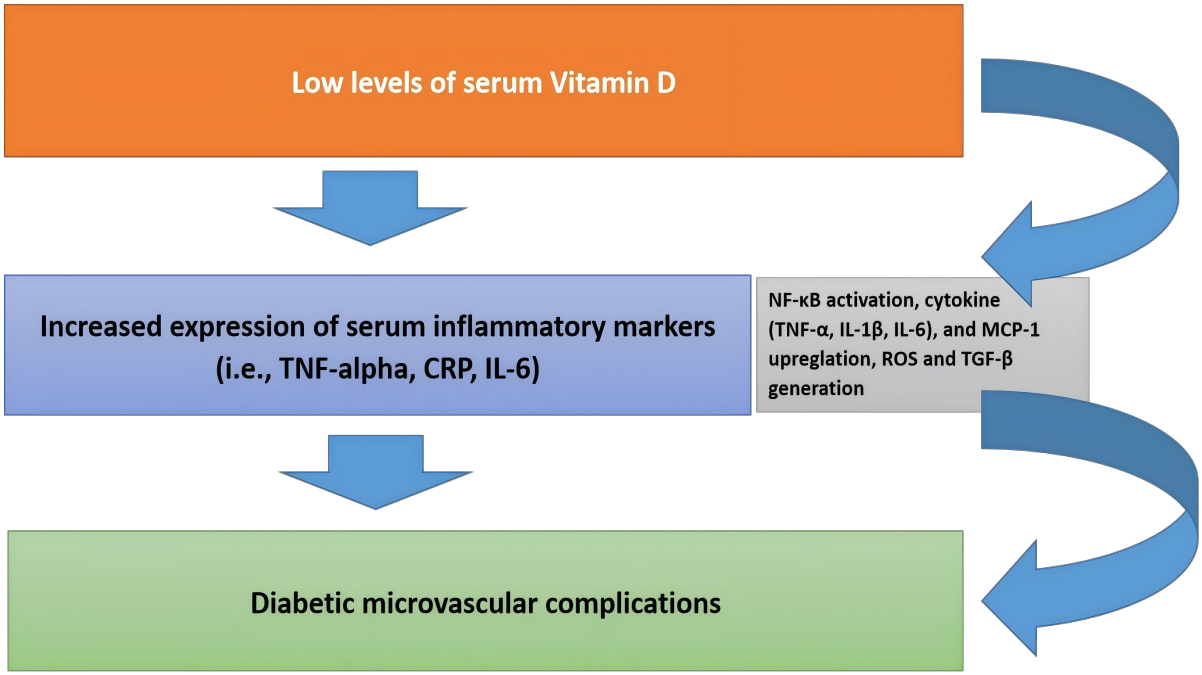

Figure 1. Mechanistic association between vitamin D and diabetes mellitus and its complications.

6. Conclusion

A significant association between vitamin D deficiency and an increased risk of developing diabetes, particularly T2DM, is well established. Vitamin D plays a crucial role in insulin sensitivity, glucose metabolism, and overall endocrine regulation. However, the precise mechanisms and causal pathways linking vitamin D status to diabetes remain incompletely understood. Future research should prioritize large-scale, RCTs stratified by baseline vitamin D status, genetic polymorphisms in the VDR and vitamin D–metabolizing enzymes, and metabolic phenotypes to clarify the efficacy and optimal dosing of vitamin D supplementation in diabetes prevention and management. Moreover, mechanistic studies employing multi-omics approaches, such as transcriptomic and metabolomic profiling, could help elucidate how vitamin D modulates insulin signaling, beta-cell function, and inflammatory pathways. Collectively, these investigations may translate current associative evidence into actionable strategies for personalized diabetes care and prevention.

Conflict of Interest

The author declares no conflict of interest.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

References

[1] Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. Immunity, 2022, 55(1), 31-55. DOI: 10.1016/j.immuni.2021.12.013

[2] Chawla A, Nguyen KD, Goh YP. Macrophage-mediated inflammation in metabolic disease. Nature Reviews Immunology, 2011, 11(11), 738-749. DOI: 10.1038/nri3071

[3] Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. Nutrients, 2013, 5(7), 2502-2521. DOI: 10.3390/nu5072502

[4] Holick MF. Vitamin D deficiency. The New England Journal of Medicine, 2007, 357(3), 266-281. DOI: 10.1056/NEJMra070553

[5] Erkus E, Aktas G, Kocak MZ, Duman TT, Atak BM, Savli H. Diabetic regulation of subjects with type 2 diabetes mellitus is associated with serum vitamin D levels. Revista da Associacao Medica Brasileira (1992), 2019, 65(1), 51-55. DOI: 10.1590/1806-9282.65.1.51

[6] Chokhandre MK, Mahmoud MI, Hakami T, Jafer M, Inamdar AS. Vitamin D & its analogues in type 2 diabetic nephropathy: a systematic review. Journal of Diabetes and Metabolic Disorders, 2015, 14, 58. DOI: 10.1186/s40200-015-0186-6

[7] Delrue C, Speeckaert R, Delanghe JR, Speeckaert MM. The role of vitamin D in diabetic nephropathy: A translational approach. International Journal of Molecular Sciences, 2022, 23(2), 807. DOI: 10.3390/ijms23020807

[8] Penna-Martinez M, Badenhoop K. Inherited variation in vitamin D Genes and type 1 diabetes predisposition. Genes, 2017, 8(4), 125. DOI: 10.3390/genes8040125

[9] Pike JW, Meyer MB, Lee SM, Onal M, Benkusky NA. The vitamin D receptor: contemporary genomic approaches reveal new basic and translational insights. The Journal of Clinical Investigation, 2017, 127(4), 1146-1154. DOI: 10.1172/jci88887

[10] Song Z, Xiao C, Jia X, Luo C, Shi L, Xia R, et al. Vitamin D/VDR Protects Against Diabetic Kidney Disease by Restoring Podocytes Autophagy. Diabetes, Metabolic Syndrome and Obesity : Targets and Therapy, 2021, 14, 1681-1693. DOI: 10.2147/dmso.s303018

[11] Uitterlinden AG, Fang Y, Van Meurs JB, Pols HA, Van Leeuwen JP. Genetics and biology of vitamin D receptor polymorphisms. Gene, 2004, 338(2), 143-156. DOI: 10.1016/j.gene.2004.05.014

[12] Wang H, Wang J, Qu H, Wei H, Ji B, Yang Z, et al. In vitro and in vivo inhibition of mTOR by 1,25-dihydroxyvitamin D(3) to improve early diabetic nephropathy via the DDIT4/TSC2/mTOR pathway. Endocrine, 2016, 54(2), 348-359. DOI: 10.1007/s12020-016-0999-1

[13] Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. The Journal of Clinical Investigation, 2006, 116(7), 1793-1801. DOI: 10.1172/jci29069

[14] Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nature reviews Immunology, 2011, 11(2), 85-97. DOI: 10.1038/nri2921

[15] O'Rourke RW, White AE, Metcalf MD, Olivas AS, Mitra P, Larison WG, et al. Hypoxia-induced inflammatory cytokine secretion in human adipose tissue stromovascular cells. Diabetologia, 2011, 54(6), 1480-1490. DOI: 10.1007/s00125-011-2103-y

[16] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. The Journal of Clinical Investigation, 2003, 112(12), 1796-1808. DOI: 10.1172/jci19246

[17] Skurk T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. The Journal of Clinical Endocrinology and Metabolism, 2007, 92(3), 1023-1033. DOI: 10.1210/jc.2006-1055

[18] Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. Diabetes Research and Clinical Practice, 2005, 69(1), 29-35. DOI: 10.1016/j.diabres.2004.11.007

[19] Chadt A, Scherneck S, Joost HG, Al-Hasani H. Molecular links between Obesity and Diabetes: “Diabesity”. Endotext. South Dartmouth (MA): MDText.com, Inc. 2000.

[20] Dula SB, Jecmenica M, Wu R, Jahanshahi P, Verrilli GM, Carter JD, et al. Evidence that low-grade systemic inflammation can induce islet dysfunction as measured by impaired calcium handling. Cell Calcium, 2010, 48(2-3), 133-142. DOI: 10.1016/j.ceca.2010.07.007

[21] Ramadan JW, Steiner SR, O'Neill CM, Nunemaker CS. The central role of calcium in the effects of cytokines on beta-cell function: implications for type 1 and type 2 diabetes. Cell Calcium, 2011, 50(6), 481-490. DOI: 10.1016/j.ceca.2011.08.005

[22] Osborn O, Brownell SE, Sanchez-Alavez M, Salomon D, Gram H, Bartfai T. Treatment with an Interleukin 1 beta antibody improves glycemic control in diet-induced obesity. Cytokine, 2008, 44(1), 141-148. DOI: 10.1016/j.cyto.2008.07.004

[23] Westermark P, Andersson A, Westermark GT. Islet amyloid polypeptide, islet amyloid, and diabetes mellitus. Physiological Reviews, 2011, 91(3), 795-826. DOI: 10.1152/physrev.00042.2009

[24] Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. Circulation, 2003, 108(19), 2317-2322. DOI: 10.1161/01.cir.0000097109.90783.FC

[25] Koukkunen H, Penttilä K, Kemppainen A, Halinen M, Penttila I, Rantanen T, et al. C-reactive protein, fibrinogen, interleukin-6 and tumour necrosis factor-alpha in the prognostic classification of unstable angina pectoris. Annals of Medicine, 2001, 33(1), 37-47. DOI: 10.3109/07853890109002058

[26] Blake GJ, Ridker PM. High sensitivity C-reactive protein for predicting cardiovascular disease: an inflammatory hypothesis. European Heart Journal, 2001, 22(5), 349-352. DOI: 10.1053/euhj.2000.2280

[27] Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. The New England journal of medicine, 2002, 347(20), 1557-1565. DOI: 10.1056/NEJMoa021993

[28] Rifai N, Ridker PM. High-sensitivity C-reactive protein: a novel and promising marker of coronary heart disease. Clinical Chemistry, 2001, 47(3), 403-411.

[29] Iademarco MF, McQuillan JJ, Dean DC. Vascular cell adhesion molecule 1: contrasting transcriptional control mechanisms in muscle and endothelium. Proceedings of the National Academy of Sciences of the United States of America, 1993, 90(9), 3943-3947. DOI: 10.1073/pnas.90.9.3943

[30] Landry DB, Couper LL, Bryant SR, Lindner V. Activation of the NF-kappa B and I kappa B system in smooth muscle cells after rat arterial injury. Induction of vascular cell adhesion molecule-1 and monocyte chemoattractant protein-1. The American Journal of Pathology, 1997, 151(4), 1085-1095.
[31] Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis, 2000, 148(2), 209-214. DOI: 10.1016/s0021-9150(99)00463-3
[32] Deiuliis J, Shah Z, Shah N, Needleman B, Mikami D, Narula V, et al. Visceral adipose inflammation in obesity is associated with critical alterations in tregulatory cell numbers. PloS one, 2011, 6(1), e16376. DOI: 10.1371/journal.pone.0016376
[33] Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nature Medicine, 2009, 15(8), 914-920. DOI: 10.1038/nm.1964
[34] Winer S, Chan Y, Paltser G, Truong D, Tsui H, Bahrami J, et al. Normalization of obesity-associated insulin resistance through immunotherapy. Nature Medicine, 2009, 15(8), 921-929. DOI: 10.1038/nm.2001
[35] Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, et al. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nature medicine, 2009, 15(8), 930-939. DOI: 10.1038/nm.2002
[36] Esser N, L'Homme L, De Roover A, Kohnen L, Scheen AJ, Moutschen M, et al. Obesity phenotype is related to NLRP3 inflammasome activity and immunological profile of visceral adipose tissue. Diabetologia, 2013, 56(11), 2487-2497. DOI: 10.1007/s00125-013-3023-9
[37] Fujisaka S, Usui I, Bukhari A, Ikutani M, Oya T, Kanatani Y, et al. Regulatory mechanisms for adipose tissue M1 and M2 macrophages in diet-induced obese mice. Diabetes, 2009, 58(11), 2574-2582. DOI: 10.2337/db08-1475
[38] Niewczas MA, Pavkov ME, Skupien J, Smiles A, Md Dom ZI, Wilson JM, et al. A signature of circulating inflammatory proteins and development of end-stage renal disease in diabetes. Nature medicine, 2019, 25(5), 805-813. DOI: 10.1038/s41591-019-0415-5
[39] Schena FP, Gesualdo L. Pathogenetic mechanisms of diabetic nephropathy. Journal of the American Society of Nephrology, 2005, 16 Suppl 1, S30-33. DOI: 10.1681/asn.2004110970
[40] Wada J, Makino H. Innate immunity in diabetes and diabetic nephropathy. Nature Reviews Nephrology, 2016, 12(1), 13-26. DOI: 10.1038/nrneph.2015.175
[41] Chow F, Ozols E, Nikolic-Paterson DJ, Atkins RC, Tesch GH. Macrophages in mouse type 2 diabetic nephropathy: correlation with diabetic state and progressive renal injury. Kidney international, 2004, 65(1), 116-128. DOI: 10.1111/j.1523-1755.2004.00367.x
[42] Chow FY, Nikolic-Paterson DJ, Atkins RC, Tesch GH. Macrophages in streptozotocin-induced diabetic nephropathy: potential role in renal fibrosis. Nephrology, Dialysis, Transplantation, 2004, 19(12), 2987-2996. DOI: 10.1093/ndt/gfh441
[43] Galkina E, Ley K. Leukocyte recruitment and vascular injury in diabetic nephropathy. Journal of the American Society of Nephrology, 2006, 17(2), 368-377. DOI: 10.1681/asn.2005080859
[44] Nguyen D, Ping F, Mu W, Hill P, Atkins RC, Chadban SJ. Macrophage accumulation in human progressive diabetic nephropathy. Nephrology (Carlton), 2006, 11(3), 226-231. DOI: 10.1111/j.1440-1797.2006.00576.x
[45] Shikata K, Makino H. Role of macrophages in the pathogenesis of diabetic nephropathy. Contributions to Nephrology, 2001, (134), 46-54. DOI: 10.1159/000060147
[46] Catalán V, Gómez-Ambrosi J, Ramirez B, Rotellar F, Pastor C, Silva C, et al. Proinflammatory cytokines in obesity: impact of type 2 diabetes mellitus and gastric bypass. Obesity Surgery, 2007, 17(11), 1464-1474. DOI: 10.1007/s11695-008-9424-z
[47] Kim CS, Park HS, Kawada T, Kim JH, Lim D, Hubbard NE, et al. Circulating levels of MCP-1 and IL-8 are elevated in human obese subjects and associated with obesity-related parameters. International Journal of Obesity (Lond), 2006, 30(9), 1347-1355. DOI: 10.1038/sj.ijo.0803259
[48] King GL. The role of inflammatory cytokines in diabetes and its complications. Journal of Periodontology, 2008, 79(8 Suppl), 1527-1534. DOI: 10.1902/jop.2008.080246
[49] McCarty MF. Adjuvant strategies for prevention of glomerulosclerosis. Medical Hypotheses, 2006, 67(6), 1277-1296. DOI: 10.1016/j.mehy.2004.11.048
[50] Soto I, Krebs MP, Reagan AM, Howell GR. Vascular Inflammation Risk Factors in Retinal Disease. Annual Review of Vision Science, 2019, 5, 99-122. DOI: 10.1146/annurev-vision-091517-034416
[51] Dai Y, Wu Z, Wang F, Zhang Z, Yu M. Identification of chemokines and growth factors in proliferative diabetic retinopathy vitreous. Biomed Research International, 2014, 2014, 486386. DOI: 10.1155/2014/486386
[52] Olson JA, Whitelaw CM, McHardy KC, Pearson DW, Forrester JV. Soluble leucocyte adhesion molecules in diabetic retinopathy stimulate retinal capillary endothelial cell migration. Diabetologia, 1997, 40(10), 1166-1171. DOI: 10.1007/s001250050802
[53] Baum P, Toyka KV, Blüher M, Kosacka J, Nowicki M. Inflammatory Mechanisms in the Pathophysiology of Diabetic Peripheral Neuropathy (DN)-New Aspects. International Journal of Molecular Sciences, 2021, 22(19), 10835. DOI: 10.3390/ijms221910835
[54] Dattola A, Silvestri M, Bennardo L, Passante M, Scali E, Patruno C, et al. Role of vitamins in skin health: A systematic review. Current Nutrition Reports, 2020, 9(3), 226-235. DOI: 10.1007/s13668-020-00322-4
[55] Pieńkowska A, Janicka J, Duda M, Dzwonnik K, Lip K, Mędza A, et al. Controversial impact of vitamin D supplementation on reducing insulin resistance and prevention of type 2 diabetes in patients with prediabetes: A systematic review. Nutrients, 2023, 15(4), 983. DOI: 10.3390/nu15040983
[56] Adams JS, Rafison B, Witzel S, Reyes RE, Shieh A, Chun R, et al. Regulation of the extrarenal CYP27B1-hydroxylase. The Journal of Steroid Biochemistry and Molecular Biology, 2014, 144 Pt A, 22-27. DOI: 10.1016/j.jsbmb.2013.12.009
[57] Haussler MR, Haussler CA, Jurutka PW, Thompson PD, Hsieh JC, Remus LS, et al. The vitamin D hormone and its nuclear receptor: molecular actions and disease states. The Journal of Endocrinology, 1997, 154 Suppl, S57-73.
[58] Klopot A, Hance KW, Peleg S, Barsony J, Fleet JC. Nucleo-cytoplasmic cycling of the vitamin D receptor in the enterocyte-like cell line, Caco-2. Journal of Cellular Biochemistry, 2007, 100(3), 617-628. DOI: 10.1002/jcb.21087
[59] Argano C, Natoli G, Mularo S, Nobili A, Monaco ML, Mannucci PM, et al. Impact of diabetes mellitus and its comorbidities on elderly patients hospitalized in internal medicine wards: data from the RePoSi registry. Healthcare (Basel), 2022, 10(1), 86 DOI: 10.3390/healthcare10010086

[60] Helming L, Böse J, Ehrchen J, Schiebe S, Frahm T, Geffers R, et al. 1alpha,25-Dihydroxyvitamin D3 is a potent suppressor of interferon gamma-mediated macrophage activation. Blood, 2005, 106(13), 4351-4358. DOI: 10.1182/blood-2005-03-1029
[61] Bikle DD. Vitamin D Regulation of Immune Function. Current Osteoporosis Reports, 2022, 20(3), 186-193. DOI: 10.1007/s11914-022-00732-z
[62] Saponaro F, Saba A, Zucchi R. An Update on Vitamin D Metabolism. International Journal of Molecular Sciences, 2020, 21(18), 6573. DOI: 10.3390/ijms21186573
[63] Cantorna MT, Arora J. Two lineages of immune cells that differentially express the vitamin D receptor. The Journal of Steroid Biochemistry and Molecular Biology, 2023, 228, 106253. DOI: 10.1016/j.jsbmb.2023.106253
[64] Ao T, Kikuta J, Ishii M. The Effects of vitamin D on immune system and inflammatory diseases. Biomolecules, 2021, 11(11). DOI: 10.3390/biom11111624
[65] Chen Y, Zhang J, Ge X, Du J, Deb DK, Li YC. Vitamin D receptor inhibits nuclear factor κB activation by interacting with IκB kinase β protein. The Journal of Biological Chemistry, 2013, 288(27), 19450-19458. DOI: 10.1074/jbc.M113.467670
[66] Zhang Y, Leung DY, Richers BN, Liu Y, Remigio LK, Riches DW, et al. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. Journal of Immunology, 2012, 188(5), 2127-2135. DOI: 10.4049/jimmunol.1102412
[67] Chen X, Zhou M, Yan H, Chen J, Wang Y, Mo X. Association of serum total 25-hydroxy-vitamin D concentration and risk of all-cause, cardiovascular and malignancies-specific mortality in patients with hyperlipidemia in the United States. Frontiers in Nutrition, 2022, 9, 971720. DOI: 10.3389/fnut.2022.971720
[68] Khademi Z, Hamedi-Shahraki S, Amirkhizi F. Vitamin D insufficiency is associated with inflammation and deregulation of adipokines in patients with metabolic syndrome. BMC Endocrine Disorders, 2022, 22(1), 223. DOI: 10.1186/s12902-022-01141-0
[69] Maddaloni E, Cavallari I, Napoli N, Conte C. Vitamin D and Diabetes Mellitus. Frontiers of Hormone research, 2018, 50, 161-176. DOI: 10.1159/000486083
[70] Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. European Journal of Clinical Nutrition, 2011, 65(9), 1005-1015. DOI: 10.1038/ejcn.2011.118
[71] Targher G, Bertolini L, Scala L, Cigolini M, Zenari L, Falezza G, et al. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. Nutrition, Metabolism, and Cardiovascular Diseases, 2007, 17(7), 517-524. DOI: 10.1016/j.numecd.2006.04.002
[72] Teleni L, Baker J, Koczwara B, Kimlin MG, Walpole E, Tsai K, et al. Clinical outcomes of vitamin D deficiency and supplementation in cancer patients. Nutrition Reviews, 2013, 71(9), 611-621. DOI: 10.1111/nure.12047
[73] Umar M, Sastry KS, Chouchane AI. Role of Vitamin D Beyond the Skeletal Function: A Review of the Molecular and Clinical Studies. International Journal of Molecular Sciences, 2018, 19(6), 1618. DOI: 10.3390/ijms19061618
[74] Wimalawansa SJ. Non-musculoskeletal benefits of vitamin D. The Journal of Steroid Biochemistry and Molecular Biology, 2018, 175, 60-81. DOI: 10.1016/j.jsbmb.2016.09.016
[75] Cade C, Norman AW. Rapid normalization/stimulation by 1,25-dihydroxyvitamin D3 of insulin secretion and glucose tolerance in the vitamin D-deficient rat. Endocrinology, 1987, 120(4), 1490-1497. DOI: 10.1210/endo-120-4-1490
[76] Chertow BS, Sivitz WI, Baranetsky NG, Clark SA, Waite A, Deluca HF. Cellular mechanisms of insulin release: the effects of vitamin D deficiency and repletion on rat insulin secretion. Endocrinology, 1983, 113(4), 1511-1518. DOI: 10.1210/endo-113-4-1511
[77] Kadowaki S, Norman AW. Dietary vitamin D is essential for normal insulin secretion from the perfused rat pancreas. The Journal of Clinical Investigation, 1984, 73(3), 759-766. DOI: 10.1172/jci111269
[78] Norman AW, Frankel JB, Heldt AM, Grodsky GM. Vitamin D deficiency inhibits pancreatic secretion of insulin. Science, 1980, 209(4458), 823-825. DOI: 10.1126/science.6250216
[79] Tanaka Y, Seino Y, Ishida M, Yamaoka K, Yabuuchi H, Ishida H, et al. Effect of vitamin D3 on the pancreatic secretion of insulin and somatostatin. Acta endocrinologica, 1984, 105(4), 528-533. DOI: 10.1530/acta.0.1050528
[80] Bourlon PM, Faure-Dussert A, Billaudel B. The de novo synthesis of numerous proteins is decreased during vitamin D3 deficiency and is gradually restored by 1, 25-dihydroxyvitamin D3 repletion in the islets of langerhans of rats. The Journal of Endocrinology, 1999, 162(1), 101-109. DOI: 10.1677/joe.0.1620101
[81] Cade C, Norman AW. Vitamin D3 improves impaired glucose tolerance and insulin secretion in the vitamin D-deficient rat in vivo. Endocrinology, 1986, 119(1), 84-90. DOI: 10.1210/endo-119-1-84
[82] Clark SA, Stumpf WE, Sar M. Effect of 1,25 dihydroxyvitamin D3 on insulin secretion. Diabetes, 1981, 30(5), 382-386. DOI: 10.2337/diab.30.5.382
[83] Bland R, Markovic D, Hills CE, Hughes SV, Chan SL, Squires PE, et al. Expression of 25-hydroxyvitamin D3-1alpha-hydroxylase in pancreatic islets. The Journal of steroid biochemistry and molecular biology, 2004, 89-90(1-5), 121-125. DOI: 10.1016/j.jsbmb.2004.03.115
[84] Sergeev IN, Rhoten WB. 1,25-Dihydroxyvitamin D3 evokes oscillations of intracellular calcium in a pancreatic beta-cell line. Endocrinology, 1995, 136(7), 2852-2861. DOI: 10.1210/endo.136.7.7789310
[85] Milner RD, Hales CN. The role of calcium and magnesium in insulin secretion from rabbit pancreas studied in vitro. Diabetologia, 1967, 3(1), 47-49. DOI: 10.1007/bf01269910
[86] Fujita T, Sakagami Y, Tomita T, Okamoto Y, Oku H. Insulin secretion after oral calcium load. Endocrinologia japonica, 1978, 25(6), 645-648. DOI: 10.1507/endocrj1954.25.645
[87] Gedik O, Zileli MS. Effects of hypocalcemia and theophylline on glucose tolerance and insulin release in human beings. Diabetes, 1977, 26(9), 813-819. DOI: 10.2337/diab.26.9.813
[88] Yasuda K, Hurukawa Y, Okuyama M, Kikuchi M, Yoshinaga K. Glucose tolerance and insulin secretion in patients with parathyroid disorders. Effect of serum calcium on insulin release. The New England Journal of Medicine, 1975, 292(10), 501-504. DOI: 10.1056/nejm197503062921003
[89] Johnson JA, Grande JP, Roche PC, Kumar R. Immunohistochemical localization of the 1,25(OH)2D3 receptor and calbindin D28k in human and rat pancreas. The American Journal of Physiology, 1994, 267(3 Pt 1), E356-360. DOI: 10.1152/ajpendo.1994.267.3.E356

[90] Kadowaki S, Norman AW. Pancreatic vitamin D-dependent calcium binding protein: biochemical properties and response to vitamin D. Archives of Biochemistry and Biophysics, 1984, 233(1), 228-236. DOI: 10.1016/0003-9861(84)90621-0
[91] Sooy K, Schermerhorn T, Noda M, Surana M, Rhoten WB, Meyer M, et al. Calbindin-D(28k) controls [Ca(2+)](i) and insulin release. Evidence obtained from calbindin-d(28k) knockout mice and beta cell lines. Journal of Biological Chemistry, 1999, 274(48), 34343-34349. DOI: 10.1074/jbc.274.48.34343
[92] Zeitz U, Weber K, Soegiarto DW, Wolf E, Balling R, Erben RG. Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. FASEB Journal, 2003, 17(3), 509-511. DOI: 10.1096/fj.02-0424fje
[93] Giulietti A, van Etten E, Overbergh L, Stoffels K, Bouillon R, Mathieu C. Monocytes from type 2 diabetic patients have a pro-inflammatory profile. 1,25-Dihydroxyvitamin D(3) works as anti-inflammatory. Diabetes Research and Clinical Practice, 2007, 77(1), 47-57. DOI: 10.1016/j.diabres.2006.10.007
[94] Gysemans CA, Cardozo AK, Callewaert H, Giulietti A, Hulshagen L, Bouillon R, et al. 1,25-Dihydroxyvitamin D3 modulates expression of chemokines and cytokines in pancreatic islets: implications for prevention of diabetes in nonobese diabetic mice. Endocrinology, 2005, 146(4), 1956-1964. DOI: 10.1210/en.2004-1322
[95] Riachy R, Vandewalle B, Kerr Conte J, Moerman E, Sacchetti P, Lukowiak B, et al. 1,25-dihydroxyvitamin D3 protects RINm5F and human islet cells against cytokine-induced apoptosis: implication of the antiapoptotic protein A20. Endocrinology, 2002, 143(12), 4809-4819. DOI: 10.1210/en.2002-220449
[96] van Etten E, Mathieu C. Immunoregulation by 1,25-dihydroxyvitamin D3: basic concepts. The Journal of Steroid Biochemistry and Molecular Biology, 2005, 97(1-2), 93-101. DOI: 10.1016/j.jsbmb.2005.06.002
[97] Riachy R, Vandewalle B, Moerman E, Belaich S, Lukowiak B, Gmyr V, et al. 1,25-Dihydroxyvitamin D3 protects human pancreatic islets against cytokine-induced apoptosis via down-regulation of the Fas receptor. Apoptosis, 2006, 11(2), 151-159. DOI: 10.1007/s10495-006-3558-z
[98] Oh J, Weng S, Felton SK, Bhandare S, Riek A, Butler B, et al. 1,25(OH)2 vitamin d inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. Circulation, 2009, 120(8), 687-698. DOI: 10.1161/circulationaha.109.856070
[99] Song Y, Wang L, Pittas AG, Del Gobbo LC, Zhang C, Manson JE, et al. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care, 2013, 36(5), 1422-1428. DOI: 10.2337/dc12-0962
[100] Pittas AG, Dawson-Hughes B, Sheehan P, Ware JH, Knowler WC, Aroda VR, et al. Vitamin D supplementation and prevention of type 2 diabetes. The New England Journal of Medicine, 2019, 381(6), 520-530. DOI: 10.1056/NEJMoa1900906
[101] LeBlanc ES, Pratley RE, Dawson-Hughes B, Staten MA, Sheehan PR, Lewis MR, et al. Baseline characteristics of the vitamin D and type 2 diabetes (D2d) study: A contemporary prediabetes cohort that will inform diabetes prevention efforts. Diabetes Care, 2018, 41(8), 1590-1599. DOI: 10.2337/dc18-0240
[102] Farahmand MA, Daneshzad E, Fung TT, Zahidi F, Muhammadi M, Bellissimo N, et al. What is the impact of vitamin D supplementation on glycemic control in people with type-2 diabetes: a systematic review and meta-analysis of randomized controlled trails. BMC Endocrine Disorders, 2023, 23(1), 15. DOI: 10.1186/s12902-022-01209-x
[103] Pittas AG, Jorde R, Kawahara T, Dawson-Hughes B. Vitamin D Supplementation for Prevention of Type 2 Diabetes Mellitus: To D or Not to D? The Journal of Clinical Endocrinology and Metabolism, 2020, 105(12), 3721-3733. DOI: 10.1210/clinem/dgaa594
[104] Dawson-Hughes B, Staten MA, Knowler WC, Nelson J, Vickery EM, LeBlanc ES, et al. intratrial exposure to vitamin D and new-onset diabetes among adults with prediabetes: A secondary analysis from the vitamin D and type 2 diabetes (D2d) study. Diabetes Care, 2020, 43(12), 2916-2922. DOI: 10.2337/dc20-1765
[105] Rani P, Koulmane Laxminarayana SL, Swaminathan SM, Nagaraju SP, Bhojaraja MV, Shetty S, et al. TGF-β: elusive target in diabetic kidney disease. Renal Failure, 2025, 47(1), 2483990. DOI: 10.1080/0886022x.2025.2483990
[106] Deb DK, Chen Y, Zhang Z, Zhang Y, Szeto FL, Wong KE, et al. 1,25-Dihydroxyvitamin D3 suppresses high glucose-induced angiotensinogen expression in kidney cells by blocking the NF-{kappa}B pathway. American Journal of Physiology Renal Physiology, 2009, 296(5), F1212-1218. DOI: 10.1152/ajprenal.00002.2009
[107] Huang HY, Lin TW, Hong ZX, Lim LM. Vitamin D and Diabetic Kidney Disease. International Journal of Molecular Sciences, 2023, 24(4), 3751. DOI: 10.3390/ijms24043751
[108] Wang Y, Deb DK, Zhang Z, Sun T, Liu W, Yoon D, et al. Vitamin D receptor signaling in podocytes protects against diabetic nephropathy. Journal of the American Society of Nephrology, 2012, 23(12), 1977-1986. DOI: 10.1681/asn.2012040383
[109] Wang Y, Yang S, Zhou Q, Zhang H, Yi B. Effects of Vitamin D Supplementation on Renal Function, Inflammation and Glycemic Control in Patients with Diabetic Nephropathy: a Systematic Review and Meta-Analysis. Kidney and Blood Pressure Research, 2019, 44(1), 72-87. DOI: 10.1159/000498838
[110] Lu L, Lu Q, Chen W, Li J, Li C, Zheng Z. Vitamin D(3) Protects against Diabetic Retinopathy by Inhibiting High-Glucose-Induced Activation of the ROS/TXNIP/NLRP3 Inflammasome Pathway. Journal of Diabetes Research, 2018, 2018, 8193523. DOI: 10.1155/2018/8193523
[111] Tecilazich F, Formenti AM, Giustina A. Role of vitamin D in diabetic retinopathy: Pathophysiological and clinical aspects. Reviews in Endocrine & Metabolic Disorders, 2021, 22(4), 715-727. DOI: 10.1007/s11154-020-09575-4
[112] Dervis N, Jurja S, Chisnoiu T, Mihai CM, Stoica AM. Serum Vitamin D Levels as Predictors of Response to Intravitreal Anti-VEGF Therapy in Diabetic Macular Edema: A Clinical Correlation Study. International Journal of Molecular Sciences, 2025, 26(17), 8481. DOI: 10.3390/ijms26178481
[113] Cheng Y, Chen Y, Li K, Liu S, Pang C, Gao L, et al. How inflammation dictates diabetic peripheral neuropathy: An enlightening review. CNS Neuroscience & Therapeutics, 2024, 30(4), e14477. DOI: 10.1111/cns.14477
[114] Hao W, Tashiro S, Hasegawa T, Sato Y, Kobayashi T, Tando T, et al. Hyperglycemia Promotes Schwann Cell De-differentiation and De-myelination via Sorbitol Accumulation and Igf1 Protein Down-regulation. Journal of Biological Chemistry, 2015, 290(28), 17106-17115. DOI: 10.1074/jbc.M114.631291
[115] Román-Pintos LM, Villegas-Rivera G, Rodríguez-Carrizalez AD, Miranda-Díaz AG, Cardona-Muñoz EG. Diabetic Polyneuropathy in Type 2 Diabetes Mellitus: Inflammation, Oxidative Stress, and Mitochondrial Function. Journal of Diabetes Research, 2016, 2016, 3425617. DOI: 10.1155/2016/3425617