

# The Importance of Vitamin D And Calcium in Type 2 Diabetes

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**Abstract.** The investigation into the involvement of vitamin D in the pathogenesis and prevention of type 2 diabetes has garnered widespread scholarly attention. Notably, vitamin D receptors are discernible in pancreatic beta cells and immune cells. In addition to its established function as the primary regulator of calcium absorption, vitamin D exerts influence on the activity of calcium-associated endopeptidases in beta cells, facilitating the conversion of proinsulin to insulin and augmenting insulin production. Within peripheral insulin target tissues, vitamin D governs insulin action through the modulation of calcium homeostasis. Further, vitamin D exhibits pronounced immunosuppressive properties. Noteworthy is the potential implication of vitamin D deficiency in the etiology of type 2 diabetes, manifesting in the inhibition of insulin secretion and enhancement of glucose tolerance. The article underscores the imperative for comprehensive research and clinical trials elucidating the multifaceted roles of vitamin D and calcium in maintaining a robust physiological framework. Insightful findings from studies conducted in Uzbekistan and globally underscore a prevailing inadequacy in the dietary intake of calcium and vitamin D among diverse populations, taking into account geographical, ethnic, and physiological variances. Emphasis is placed on the critical significance of sustaining optimal levels of calcium and vitamin D for skeletal health, particularly in the context of osteoporosis prevention and treatment.

**Keywords:** Vitamin D, calcium, type 2 diabetes, insulin, glucose tolerance, menopause, postmenopause, osteoporosis

Diabetes mellitus, an omnipresent metabolic disorder, exerts a profound impact on virtually all organ systems. Its escalating global prevalence has catapulted it into a paramount health concern, particularly within highly developed nations. Emerging as a predominant chronic ailment, the worldwide incidence of diabetes exhibits a relentless upward trajectory, with over 380 million individuals affected. Annual increments of 5-7% and a doubling rate every 10-12 years underscore the gravity of its progression. Projections indicate that if this trend persists, the affected population may soar to approximately 560 million by 2030 (IDF Diabetes Atlas 10th edition, 2022).

In-depth epidemiological investigations conducted as of January 1, 2019, uncovered that 230,610 individuals in Uzbekistan were registered with diabetes. Among them, 18,349 had Type 1 diabetes (T1D), and 212,261 had Type 2 diabetes (T2D). Recent screenings disclose a 1.6-fold increase in the prevalence of T2D over the past 14 years in Uzbekistan, reaching 7.9% among individuals aged 35 and older (2015 data). The unregistered or undiagnosed cases, coupled with the subclinical manifestations of the disease, further contribute to the overall apprehension (Clinical recommendations for the treatment of type 2 diabetes, 2019).

The year 2020 witnessed diabetes contributing to 6,205 deaths in Uzbekistan, constituting 3.84% of total mortality (World Health Organization, 2020). As of April 2, 2022, 6.3% of the elderly population in Uzbekistan is affected by diabetes. Projected figures for 2023 estimate a total of 363,585 affected individuals, with 15% having T1D and the remaining 85% having T2D. Among these, 15% necessitate continuous insulin injections, while others manage the condition through dietary restrictions and medications that modulate physical activity and regulate blood sugar levels. Of note, nearly half of the individuals affected by diabetes are women ([www.idf.org](http://www.idf.org)). This comprehensive analysis delves into the multifaceted dimensions of diabetes mellitus, highlighting its intricate epidemiological landscape and the evolving strategies for management and mitigation.

At present, diabetes stands as the third most prevalent condition within the realm of hematological and oncological diseases, while asserting itself as the foremost concern among endocrine disorders. Despite considerable progress in unraveling the etiology of diabetes, its precise etiopathogenesis remains an area of

continuous scholarly discourse. Notably, factors encompassing oxidative stress, reactive oxygen species, and autoimmune reactions have surfaced as influential contributors to the underlying pathogenic processes of diabetes. Recent investigations have accentuated the substantial roles played by vitamin D and calcium in both the pathogenesis and preventive measures of diabetes (Ismoilov, 2005; Shagazatova, 2020).

On a global scale, a pronounced prevalence of vitamin D deficiency and insufficiency is evident, particularly among women residing in the Near East (81%), Asia (71.4%), and Australia (60.3%). European countries record this indicator at 57.7%, while Latin America follows closely at 53.4%. Intriguingly, in the Caucasus region, it has been observed that for each degree of latitude, the blood level of 25(OH)D experiences a decrement of 0.69 nmol/L, manifesting a gradient from north to south or south to north, originating from the equator (Hagenau *et al.*, 2018).

Calcium homeostasis is primarily regulated by vitamin D, which enhances insulin exocytosis directly or indirectly through the activation of calcium-dependent endopeptidases. Vitamin D also improves glucose tolerance (Tuorkey *et al.*, 2010). The effective antioxidant role of vitamin D offers the potential to counteract the progression of type 2 diabetes. Additionally, vitamin D stimulates the activity of steroid hormone-producing cells, inhibits cytotoxicity, macrophages, a type of advanced glycation end product, and the generation of natural killer cells (Pittas *et al.*, 2007). Vitamin D also fulfills several functions beyond calcium. It serves as a regulator for cell proliferation, differentiation, and replication, acting as a mediator in various organs and biological systems during autoimmune reactions. Studies have expanded our understanding of the physiological role of vitamin D in immune system cells (Mathieu *et al.*, 2005).

As a fat-soluble vitamin, vitamin D plays a crucial role in maintaining calcium homeostasis, preserving bone health, and reducing the risk of fractures (Ogunkolade *et al.*, 2002). To assess vitamin D status, evaluating the concentration of its metabolite, 25(OH)D in the blood, is recommended. Vitamin D deficiency is defined as a concentration below 30 ng/ml, while insufficiency is below 20 ng/ml (Speer *et al.*, 2001). Additionally, dietary sources rich in vitamin D include fish such as salmon, sardines, and tuna (Angel *et al.*, 2014). Furthermore, individuals with malabsorption or obesity-related issues may experience diminished biological availability of vitamin D from dietary sources. Conditions like liver dysfunction, intestinal diseases, and active rickets can also contribute to the impaired synthesis of active vitamin D metabolites (Reis *et al.*, 2004).

Calcium stands as one of the fundamental macrominerals in the human body. Approximately 99% of calcium is found in the skeletal system, with the remaining fraction distributed outside the cells, predominantly in bodily fluids and other tissues. Calcium is ingested into the body through diet, with the highest concentrations present in dairy products. It is excreted through feces, urine, and sweat, emphasizing the need for external supplementation. Various factors influence calcium absorption, including dietary composition, blood vitamin D levels, and vitamin D receptor genotypes. Oxalates (salts and esters of oxalic acid) decrease calcium absorption, while phytates (aromatic amino acids) diminish calcium release and increase glucose. Excessive salt and caffeine intake enhances calcium excretion through urine, contributing to increased protein catabolism in the intestines (Dawson-Hughes, 2017).

For normal calcium absorption in the intestines, an adequate level of vitamin D in the blood is crucial. Vitamin D deficiency is a widespread issue globally, impacting not only the negative calcium balance and impaired mineralization of bones but also correlating with muscle weakness and an increased risk of falls, particularly in individuals suffering from conditions such as osteoporosis (Carmeliet *et al.*, 2015).

Reaching the highest peak of bone mass, essential for adequate utilization throughout life, is one of the numerous requirements for sufficient calcium intake. During the growth period, the optimal daily calcium intake is estimated to be around 1100 mg (de Assumpção *et al.*, 2016). The peak bone mass is achieved between the ages of 25-30, after which the consolidation process of bone tissues stabilizes, maintaining balance in women until approximately 45-50 years and in men until around 55-60 years. Calcium absorption efficiency contributes to calcium homeostasis. Prolonged calcium deficiency can consistently hinder the mineralization of bone tissue, potentially increasing the risk of osteoporosis, especially in the elderly (Wilczynski and Camacho, 2014).

Type 2 diabetes and vitamin D. Characterized by insulin resistance and altered insulin secretion, type 2 diabetes exhibits seasonal variations in glycemic control, potentially linked to widespread vitamin D deficiency due to reduced sunlight exposure in late autumn and winter. Various studies underscore the

correlation between vitamin D and type 2 diabetes. In a recent investigation, de Boer et al. explored the impact of calcium and vitamin D supplementation on drug-treated diabetes mellitus in postmenopausal women, determining that the addition of these elements did not reduce diabetes incidence (Dawson-Hughes, 2017). Nevertheless, they hypothesized that higher doses of vitamin D might be necessary to influence diabetes risk. Supporting this notion, an analysis of menopausal women – major trials and observations comparing those with the lowest and highest calcium and vitamin D intake (daily > 1200 mg and > 800 IU, respectively) – revealed a 33% lower risk of type 2 diabetes. Another pivotal cohort study in Finland identified an inverse association between serum 25(OH)D<sub>3</sub> and type 2 diabetes risk. These findings align with Pittas et al.'s investigations (Pittas *et al.*, 2007; Sicree *et al.*, 2006) into postmenopausal women's health, specifically focusing on assessing the effects of additional vitamin D. However, these studies did not distinguish the impact of vitamin D deficiency on beta-cell function or insulin resistance. Multiple reports underscore the active role of vitamin D in functionally regulating beta-cells within the endocrine pancreas. Notably, beta-cells not only harbor receptors for 1,25(OH)<sub>2</sub>D<sub>3</sub> but also feature an effector portion of the vitamin D-dependent calcium-binding protein, calbindin-D28k. The expression of calbindin-D28K in beta-cells is suggested to safeguard against cell death in cytokine-mediated apoptosis, ultimately mitigating the risk of type 2 diabetes. Calbindin-D28K's biological roles extend to neurons, contributing to the regulation of calcium homeostasis and calcium-dependent signaling during the developmental process.

In conclusion, a thorough examination of research findings provides compelling evidence for the potential role of vitamin D in both the pathogenesis and prevention of diabetes. Notably, vitamin D deficiency adversely affects human beta-cell function, leading to the development of type 2 diabetes due to compromised glucose tolerance. Early-life deficiencies in both vitamin D and calcium contribute to the subsequent onset of autoimmune diabetes in humans. The interplay of various genes associated with diverse pathogenetic aspects of the disease highlights a significant association with vitamin D. Both metabolic and immune pathways related to vitamin D and calcium demonstrate potential involvement in diabetes pathogenesis, operating at both atrophic-environmental and genetic levels. Although investigations into the supplementation of vitamin D and calcium for diabetes prevention have yielded diverse outcomes, the establishment of a contributory role requires robust clinical data for conclusive validation.

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