DOBRZENIECKI, Krzysztof, HOPEJ, Natalia, MUC, Katarzyna, TUREK, Kacper, BŁASZCZYSZYN, Katarzyna, BOLEK, Monika, DARDZIŃSKA, Nicol, GRZEGORCZYK, Aleksandra and PACHLA, Magdalena. The Association between Vitamin D Deficiency and the Prognosis of Type 2 Diabetes Mellitus. Quality in Sport. 2024;22:51724. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.22.51724
https://apcz.umk.pl/QS/article/view/51724

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 25.05.2024. Revised: 20.06.2024. Accepted: 24.06.2024. Published: 06.07.2024.

The Association between Vitamin D Deficiency and the Prognosis of Type 2 Diabetes Mellitus

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Abstract:

Introduction: Type 2 diabetes mellitus is a prevalent chronic disease with high morbidity and mortality, characterized by inadequate cellular response to insulin and insufficient insulin production by pancreatic β-cells. Epidemiological studies indicate that low serum vitamin D levels are prevalent among the general population globally, exacerbating outcomes of many diseases. Recent studies suggest that vitamin D deficiency may impact type 2 diabetes mellitus prognosis. Understanding type 2 diabetes mellitus risk factors and disease progression variables is crucial for proper patient management and public health policies.

Purpose of the work: This study aims to review the relationship between vitamin D deficiency and the prognosis of type 2 diabetes mellitus.

Materials and methods: A comprehensive analysis of research papers available on PubMed, Google Scholar, Web of Science, Embase and Scopus was undertaken using the search terms encompassing the following keywords: vitamin D insufficiency / vitamin D supplementation / vitamin D_2 / vitamin D_3 / ergocalciferol / cholecalciferol and type 2 diabetes mellitus / complications of diabetes / hyperglycemia / insulin resistance / glucose metabolism.

Results: Vitamin D deficiency can impact the prognosis of type 2 diabetes mellitus, exacerbating complications associated with chronic hyperglycemia such as obesity, mental health issues, vascular complications, and diabetic neuropathy. Given its prevalence among type 2 diabetes mellitus patients, early screening and supplementation of vitamin D could offer potential benefits.

Keywords: type 2 diabetes mellitus, vitamin D deficiency, vitamin D supplementation

Introduction:

Type 2 diabetes mellitus is recognized as one of the most common chronic diseases worldwide. It is caused by a lack of appropriate cellular response of insulin-sensitive tissues to normal insulin levels and insufficient insulin production by pancreatic β-cells (1,2). Due to its association with other lifestyle diseases and the risk of developing complications that reduce both quality of life and lifespan, it poses a serious challenge in routine medical practice. Currently, approximately 529 million adults aged 20-79 suffer from diabetes, representing as much as 10.5% of the world's population in this age group, with type 2 diabetes accounting for 96% of cases (3). It is estimated that by 2045, this number will surge to 783 million. Diabetes accounts for approximately 11.3% of deaths worldwide in the mentioned age group, making it one of the most common causes of death worldwide (4,5). Consequently, diabetic patients are frequently hospitalized, not solely due to their underlying condition. According to the National Diabetes Hospital Audit, between 25 and 31% of hospitalized patients have diabetes (6). In many cases, this leads to psychological disorders such as depression, occurring 2 to 3 times more frequently in diabetic patients than in the general population (7). Consequently, affected individuals become incapacitated for work, resulting in further substantial economic losses (8). Therefore, it is crucial to comprehensively understand the risk factors as well as variables that can influence the progression of the disease.

Vitamin D deficiency is a prevalent global health concern. Recent estimates suggest that its prevalence ranges from approximately 24% of the population in the United States to 40% in Western Europe (9). Studies indicate that the majority of the population in Europe have vitamin D levels below 30-50 ng/mL, which is generally considered adequate (10). Vitamin D is fat-soluble and functions as a steroid hormone. It exists in 2 forms - inactive $25(OH)D_3$ and active $1,25(OH)_2D_3$, converted from $25(OH)D_3$ in the kidneys (11). Its primary function is to regulate calcium and phosphorus absorption and metabolism. Moreover, it influences the function of pancreatic β-cells and tissue sensitivity to insulin and exhibits immunomodulatory properties (12). Several studies have highlighted subnormal levels of vitamin D as a significant risk factor for the development of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes (13). Moreover, several recent studies have established an association between vitamin D deficiency and the prognosis of diabetes type 2. This study aims to review the relationship between these variables.

Vitamin D metabolism:

Vitamin D is a group of compounds with the common formula $C_{28}H_{43}OH$, of which the most important for humans are: vitamin D_2 (ergocalciferol), synthesized naturally in mushrooms and plants, and vitamin D_3 (cholecalciferol) found in products of animal origin. Vitamin D can be derived from endogenous synthesis, occurring in keratinocytes located in the epidermis; food products, naturally containing vitamin D such as fatty fish, eggs, animal liver, oils, dairy products, as well as dietary supplements (14). Over 80% of the active form of vitamin D comes from synthesis in the skin upon exposure to ultraviolet B radiation (UV-B). The effectiveness and extent of this process depend on the skin phenotype and age of the person, the use of personal protective products such as sunscreen, alongside geographical latitude, time of the day, season, weather conditions including cloudiness and air pollution (15). The endogenous synthesis of vitamin D is initiated by a non-enzymatic photoisomerization. The substrate for this process is a 7-dehydrocholesterol (7-DHC), present in the skin, which is converted into pre-vitamin D (pre-D_3) (16). This reaction occurs with the involvement of UV-B, occurring at wavelengths ranging from 290 to 315 nm, with the greatest intensity at 297 nm (17). Subsequently, under the body temperature conditions, pre-D_3 undergoes isomerization, catalyzed by reductase, reaching its stable form: cholecalciferol (vitamin D_3). In this form, it binds to the vitamin D binding protein (VDBP) and is transported to the liver (18). To prevent excess vitamin D serum levels in the body during intemperate exposure to UV-B, pre-vitamin D_3 is transformed into tachysterol and lumisterol (17). The hydroxylation of cholecalciferol and ergocalciferol occurs in the liver at the 25 position of the side chain, resulting in the formation of 25-hydroxyvitamin D [25(OH)D] - calcidiol (14,18). The process of hydroxylation also takes place in the kidneys, where the reaction is catalysed by 1α-hydroxylase, resulting in the formation of the active form of vitamin D – calcitriol (1,25-dihydroxycholecalciferol) (18). Eventually, calcitriol binds to the vitamin D receptor (VDR) in target tissues: bone, blood vessel walls, heart, kidney tubule cells, pancreatic cells, intestinal epithelium, as well as brain, muscles, and adrenal glands (14,17). VDR receptors act as transcription factors, belonging to the nuclear retinoid X receptor family. By binding to VDR, calcitriol regulates the transcription of genes. In the first stage of this process, a complex of calcitriol with VDR is formed, which subsequently binds to the retinoid X receptor (RXR). The VDR-RXR heterodimer binds to vitamin D responsive elements (VDRE) in the promoter regions of target genes, inhibiting or enhancing transcription of the genes (19). Genes regulated by VDR, code for proteins including cytokines, proteins essential for the functioning of pancreatic β-cell, calcium-binding proteins (CaBP), 1α-hydroxylase, 24-hydroxylase, prostate-specific antigen (PSA), parathyroid hormone (PTH), osteocytes, osteoblasts, osteoprogenitor cells, collagen, RANK receptor and its ligand RANKL, alkaline phosphatase, calbindin, complement components, growth hormone, and insulin receptor (20–23).

Vitamin D and the occurrence of type 2 diabetes mellitus:

Many studies emphasize the correlation between vitamin D levels and the occurrence of type 2 diabetes mellitus (14,18). This can be explained by the indirect influence of calcitriol on insulin secretion as well as the presence of VDR receptors in the pancreatic tissues (24). Additionally, it affects adipocyte function and cytokine production, which can be implicated in the pathogenesis of type 2 diabetes mellitus, however, further studies are required to evaluate this (14,15,25). In data collected by NHANES (National Health and Nutrition Examination Survey), a strong link between vitamin D levels and insulin resistance can be found, although correlations vary depending on the studied population (26).

In a prospective study with a median follow-up of 8.1 years and 6,940 cases of type 2 diabetes mellitus, it was demonstrated that higher serum 25-hydroxyvitamin D concentrations are associated with a lower risk of developing the disease, thereby providing better glycemic control. These outcomes are consistent with other cohort studies carried out in the past few years (27–29)._However, not all studies confirm the relationship between vitamin D deficiency and an increased risk of developing poorly controlled type 2 diabetes mellitus (30). Therefore, further research is required to better understand this association.

Vitamin D deficiency and obesity:

Approximately 10.5% of the world's population struggles with both diabetes and obesity. Studies have shown that a deficiency in vitamin D is associated with an increased risk of developing both of these conditions (14,31,32). Research demonstrates the impact of vitamin D deficiency, in conjunction with VDR gene polymorphism present in adipocytes, on the occurrence of obesity. A decreased level of vitamin D, mediated by VDR, increases the differentiation and metabolism of adipocytes, thereby favoring the development of excess fat tissue volume (33). Insulin secretion also depends on VDR in pancreatic β-cells. Vitamin D deficiency leads to inadequate receptor activation, resulting in reduced insulin secretion. This contributes to excessive lipogenesis and deposition of fat tissue (34). Additionally, a low level of vitamin D may lead to an increase in PTH, which enhances lipogenesis and inhibits lipolysis, ultimately leading to weight gain (35).

Vitamin D deficiency and mental health:

Vitamin D receptors are also present in various regions of the brain, including the hippocampus, substantia nigra, and cerebellum (36), indicating that vitamin D may influence numerous processes such as neuromodulation and brain development. Vitamin D deficiency can lead to disruptions in these functions, contributing to the onset of various psychiatric disorders. Decreased levels of vitamin D have been significantly associated with conditions including depression, schizophrenia, anxiety disorders, stress, and autism (37,38).

A recent study indicates a higher prevalence of depression symptoms among individuals exhibiting a deficiency in vitamin D and possessing at least one copy of the altered allele of the FokI gene. Additionally, vitamin D deficiency disrupts serotonin metabolism, a key neurotransmitter with significant implications for the development of depression (39).

It is suggested that a deficiency of vitamin D affects the development of autism even during pregnancy (40). Schizophrenia may manifest itself years later in adulthood due to earlier exposure to low levels of vitamin D (41). Additionally, vitamin D deficiency can negatively impact concentration and memory retention, leading to decreased learning outcomes (38).

Vitamin D deficiency and vascular complications:

Vascular complications are major contributors to the morbidity and mortality associated with diabetes mellitus (2). Understanding the pathophysiology, risk factors, and management strategies for macrovascular and microvascular complications is essential for optimizing clinical outcomes and enhancing the quality of life for individuals suffering from diabetes. Comprehensive management approaches focusing on glycemic control, blood pressure management, lipid control, lifestyle modifications, and targeted therapies are integral components of vascular complication prevention and treatment in diabetes care (42).

Examples of macrovascular complications include coronary artery disease, peripheral artery disease, and stroke. Conversely, diseases caused by impairment of capillary circulation include diabetic nephropathy and retinopathy (43).

The relationship between vitamin D and vascular complications of diabetes has been mainly studied in Asia. Researchers investigated the connection between vitamin D deficiency and diabetic vascular complications, including diabetic retinopathy, diabetic kidney disease, and diabetic foot ulcers. The study revealed that vitamin D deficiency was associated with an increased risk of diabetic foot ulcers among Chinese patients with type 2 diabetes mellitus. However, the link between vitamin D deficiency status and diabetic retinopathy or diabetic kidney disease was not significant when adjusting for all potential covariates (44). Therefore, vitamin D screening may be considered in preventing the formation of diabetic foot ulcers and reducing the rate of lower limb amputations among diabetic patients.

Diabetic nephropathy is a leading cause of chronic kidney disease. It can eventually progress to end-stage renal disease requiring dialysis or renal transplantation (45). Studies indicate that the 5-year survivability rates on dialysis average around 40-50% (46–48), which can be even lower among diabetic patients (49). Therefore, the prognosis for dialysis patients is considerably poorer compared to many types of cancer. For instance, the 5-year survival rates for prostate cancer, breast cancer, and colorectal cancer, are 83%, 82%, and 56% respectively (48). Researchers have hypothesized that low levels of vitamin D could contribute to more microvascular complications, leading to kidney damage (50). However, a study conducted in China found no significant association between low vitamin D levels and the prevalence of diabetic nephropathy (44). Nevertheless, a meta-analysis suggested a positive influence of vitamin D on albuminuria, potentially slowing down the progression of nephropathy in patients with chronic kidney disease (45). The relationship between diabetic retinopathy and vitamin D levels has also been investigated. A meta-analysis of 15 studies indicated that vitamin D deficiency was associated with a higher risk of retinopathy (51), but other studies have shown contrasting results (52).

Vitamin D deficiency and diabetic neuropathy:

Diabetic neuropathy is one of the main complications of diabetes mellitus, affecting almost half of diabetics over their lifespan. It results from hyperglycemia-induced impairment to peripheral nerves. Diabetic neuropathy can manifest even at the onset of type 2 diabetes diagnosis (53). Delayed diagnosis and treatment of diabetic neuropathy frequently culminates in lower limb amputation, leading to a marked decline in quality of life, reduced life expectancy (averaging 2 years post-amputation), and imposes a substantial economic burden (54).

Studies suggest that risk factors contributing to the onset and progression of diabetic neuropathy include age, body mass index, smoking, the duration of diabetes, estimated glomerular filtration rate (eGFR), fibrinogen levels, poor glycemic control, high-density lipoprotein and cholesterol levels, hypertension, presence of cardiovascular disease, history of foot ulcers, micro- or macroalbuminuria, and retinopathy (55,56).

Current research indicates a potential association between vitamin D deficiency and the onset of diabetic neuropathy. Studies have demonstrated significantly reduced vitamin D levels in patients presenting diabetic neuropathy compared to the control groups (57,58). Women with diabetic neuropathy exhibit notably lower levels of 25-hydroxyvitamin D compared to males (59). Moreover, patients with painful neuropathy specifically exhibit reduced levels of vitamin D possibly through the elevation of TNF-α and IL-6 levels (60,61).

The exact mechanism remains unknown, yet it entails the regulatory impact of vitamin D on the expression of neurotrophic factors, which are crucial for nerve viability and renewal. Furthermore, vitamin D potentially ceases the synthesis of pro-inflammatory cytokines, pivotal in nerve deterioration and inflammation (62).

Conclusions:

Vitamin D deficiency may affect the prognosis for individuals with type 2 diabetes mellitus. It might play a role in exacerbating various complications of chronic hyperglycemia, such as heightened risk of obesity, mental health status, microvascular and macrovascular complications, and diabetic neuropathy. Given the prevalent occurrence of vitamin D deficiency among type 2 diabetes mellitus patients, early screening and supplementation may be beneficial.

Disclosure:

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All authors have read and agreed with the published version of the manuscript.

Funding statement:

The study did not receive special funding.

Institutional review board statement:

Not applicable.

Informed consent statement:

Not applicable.

Data availability statement:

Not applicable.

Conflict of interest:

The authors declare no conflict of interest.

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