

Type 2 Diabetes Mellitus and Vitamin D: A Systematic Review of the Effects of Vitamin D Deficiency on the Outcomes and Management of Hyperglycemia

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Abstract

Diabetes mellitus is a substantial health concern worldwide, specifically Type 2 diabetes mellitus, which has become an alarming disease and has become the seventh most common disease in terms of human suffering (DALYs), with 462 million people. In Pakistan, this figure is divided according to their ages, 27.4 million for those aged 20 and over and 13.8 million for those under 20 years. T2DM is a risk factor for developing microvascular and macrovascular complications that have an adverse effect on physical and psychological health for both patients and caregivers. Various factors are involved in the prevalence of T2DM, one of which is vitamin D deficiency. Besides the role of vitamin D, it has numerous non-skeletal functions in cancer, autoimmune diseases, psoriasis, multiple sclerosis, cardiovascular disease, and type 2 diabetes. Vitamin D impacts glucose tolerance, insulin sensitivity, and pancreatic beta cell function in people at high risk for type 2 diabetes. Obesity, aging, and low physical activity are also contributing risk factors among the T2DM and vitamin D-deficient populations. In obesity, vitamin D is no longer available as it is stored in adipose tissue due to its fat-soluble properties. It is the primary cause of hypovitaminosis D. The research revealed that women are more deficient in vitamin D, and older individuals secrete more insulin after consuming glucose. Vitamin D is crucial in regulating immune functions (by enhancing monocytes to macrophage differentiation and increasing cytotoxic activities) and lipid metabolism (by enhancing fatty acid oxidation and mitochondrial metabolism) in T2DM.

Keywords: Type 2 Diabetes, Hyperglycemia, Vitamin D, Insulin Resistance, Dietary Vitamin D deficiency

Highlights

- Overweight and obesity are more common in patients with type 2 Diabetes Mellitus
- The macronutrient intake pattern of the patients was mush poor and imbalanced
- Patients with T2DM suffer from dyslipidemia
- BMI, age, and HbA1c are the strongest predictors of dyslipidemia in T2DM

1. Introduction

1.1. Diabetes Mellitus

Hyperglycemia is a symptom of diabetes mellitus, consisting of physiological dysfunctions caused by insufficient insulin secretion, excessive glucagon secretion, or insulin resistance (Blair, M., 2016). As a chronic condition, diabetes mellitus requires ongoing medical care. Diabetes mellitus is a significant burden on healthcare systems, with hundreds of millions of people suffering globally, and its incidence is steadily increasing. Recent research examining the fundamental processes underlying the development of diabetes suggests that gut barrier dysregulation plays an essential role (De Kort, et al., 2011).

1.2. Types of Diabetes Mellitus

Generally, there are three types of diabetes, viz. i) type 1 diabetes, in which the body is incapable of producing insulin and the patient must currently inject insulin or wear an insulin pump, and known as insulin-dependent diabetes mellitus (IDDM). It is also called "Juvenile diabetes", ii) type 2 diabetes, also known as non-insulin-dependent diabetic mellitus (NIDDM). Insulin resistance is a disorder in which cells do not use insulin properly, with or without a complete insulin shortage. "Adult-onset diabetes" was once used to describe this type of condition. Gestational diabetes, the third primary form, is brought on by elevated blood glucose levels in pregnant women who have never had diabetes before. It might appear before type 2 DM develops (Deshmukh et al., 2015). Additional causes of diabetes include genetic disorders, pancreatic-damaging diseases, and an excess of certain hormones, such as growth hormone and glucocorticoids; diabetes mellitus can also be caused by drugs, chemicals, or infections; correctly classifying the type of diabetes often aids in the selection of the relevant treatment (Solis-Herrera et al., 2015). Type 3 diabetes is a term used to define the hypothesis that insulin resistance in the brain causes Alzheimer's disease

1.3. Type 2 Diabetes

More than 90% of diabetic patients have type 2 diabetes, which can result in microvascular and macrovascular problems that cause significant physical and psychological distress for both patients and caregivers (Chatterjee et al., 2017). Individuals with type 2 diabetes are more susceptible to a variety of short- and long-term problems, many of which result

in their untimely death. They possess the tendency to have higher rates of morbidity and mortality due to the disease's prevalence and delayed diagnosis, particularly in developing nations with limited resources (Olokoba et al., 2012).

1.4. Global Prevalence of Type 2 Diabetes

It is estimated that 462 million people worldwide, or 6.28% of the global population, have type 2 diabetes. This disorder was the tenth greatest cause of mortality in 2017 alone, accounting for over 1 million deaths. Compared to 1990, when type 2 diabetes was the eighteenth largest cause of mortality, this is a concerning increase. Diabetes is the seventh most common disease in terms of human suffering (DALYs) (Khan et al., 2020).

1.5. Prevalence of Type 2 Diabetes in Pakistan

In Pakistan, type 2 diabetes (T2DM) is increasing rapidly. Disease development is linked to several micro- and macrovascular consequences, which raises the financial burden on patients and the nation (Zia et al., 2016). According to the IDF Diabetes Atlas 2017, Pakistan has 7.5 million cases of diabetes in the Middle East and North Africa (MENA) region, ranking it second out of 21 nations. It also has a 6.9% prevalence of diabetes in the same age range, placing it at number 18 out of 21 countries. According to the NDSP-II 2016–17, the prevalence of diabetes in Pakistan is 26.3%, meaning that there are 27.4 million cases of diabetes in those aged 20 and over. In contrast, the 13.7% pooled prevalence of diabetes suggests that 13.8 million adults in Pakistan (those aged ≥ 20) have diabetes. These pooled cases are twice as significant as cases reported by the IDF; over half of the cases were estimated from the NDSP-II; nevertheless, close to 17.1 million cases of diabetes (≥ 20 years) were obtained from prevalence of diabetes 16.98% by the DPS-PAK 2017 (Adnan & Aasim., 2020).

2. Importance of vitamin D in health

A fat-soluble hormone, vitamin D (VD), is essential for bone metabolism and calcium homeostasis and has anti-inflammatory and antioxidant qualities that affect both innate and adaptive immunity. As a result, it is currently regarded as an immunomodulating agent in science. Numerous allergy illnesses' etiopathogenesis and evolution have been demonstrated to be guided by the combined action of VD and microbiomes. The antiproliferative, antiangiogenic, and prodifferentiation activity that is unquestionably assigned to VD itself must be remembered among the several currently attributed to VD. This activity plays a part in cancer carcinogenesis that has not yet been eliminated (Murdaca & Gangemi, 2022). Numerous studies have connected VDD to poor health outcomes for pregnant mothers and children. VDD can cause nutritional rickets (NR), disruptions in calcium homeostasis, and osteomalacia, whether or not there is a dietary calcium deficiency is uncontroversial (Fiscialetti et al., 2017).

2.1. Role of Vitamin D in glycemic regulation

Vitamin D primarily controls bone metabolism and calcium and phosphorus homeostasis. Numerous non-skeletal illnesses, such as cancer, autoimmune diseases, psoriasis, multiple sclerosis, cardiovascular disease, and type 2 diabetes, may be impacted by vitamin D. The prevalence of type 2 diabetes is inversely correlated with plasma vitamin D levels. Indeed, a lack of vitamin D has been proposed as a risk factor for type 2 diabetes. According to specific research, vitamin D may have a functional impact on glucose tolerance via influencing insulin sensitivity and secretion (Saif-Elnasr et al., 2017). Vitamin D supplementation's impact on prediabetes has recently been documented (Wang et al., 2022). Vitamin D supplementation has been linked in studies to better insulin sensitivity and beta cell function in people at high risk for diabetes, but not in people with normal baseline fasting glucose. The impact of vitamin D supplementation on individuals with type 2 diabetes has been assessed in a number of randomized controlled trials (RCTs), however, the results of these studies have been inconsistent. In patients with type 2 diabetes or impaired glucose tolerance, a recent systematic review and meta-analysis revealed weak correlations between vitamin D treatment and improved insulin resistance and decreased fasting glucose (Wu et al., 2017).

2.2. Chemicals involve in the regulation of T2DM & Vitamin D

Both a decrease in antioxidant defenses and an increase in plasma-free radical production contribute to oxidative stress in diabetes. Hyperglycemia and hyperinsulinemia may cause oxidative stress and increase the generation of free radicals. Oxidative stress has been shown to be a significant factor in insulin resistance, decreased insulin production, and other consequences of diabetes, including micro- and macrovascular damage. Antioxidant enzymes such as glutathione peroxidase (GPx) and superoxide dismutase (SOD) shield the organism against oxygen-free radicals. By altering certain antioxidant enzymes, some experimental research suggested that vitamin D might have antioxidant qualities (Saif-Elnasr et al., 2017).

Insulin resistance is the first sign of diabetes. By releasing more insulin, the β -cells can overcome this resistance and avoid hyperglycemia. But when this hyperactivity rises, the β -cells receive too much Ca^{2+} and ROS signaling, which causes cell death and the development of diabetes. Both the early insulin resistance and the later onset of diabetes due to β -cell loss are influenced by vitamin D deficiency. Insulin resistance is caused mainly by inflammation, which vitamin D helps to minimize. The normal resting levels of ROS and Ca^{2+} , which are increased in the β -cells during diabetes, are maintained

by vitamin D. The maintenance of the epigenome is another important function of vitamin D. One characteristic of diabetes is epigenetic changes, whereby hypermethylation inactivates several genes linked to the disease. By boosting the expression of the DNA demethylases that stop the hypermethylation of many gene promoter regions of numerous diabetes-related genes, vitamin D works to prevent this kind of hypermethylation. Many of these systems start to deteriorate when vitamin D levels are low, paving the way for developing conditions like diabetes (Berridge, 2017).

2.3. Effect of vitamin D deficiency on type 2 Diabetes Mellitus

Several mechanisms have explained the possible involvement of vitamin D in glucose metabolism:

- 1) Direct stimulation of insulin secretion via the pancreatic beta cells' vitamin D receptor.
- 2) Reduction of systemic inflammation and consequent improvement in insulin resistance.
- 3) Amelioration of peripheral insulin resistance through the muscles' and liver's vitamin D receptors (Lee et al., 2017).

The risk factors for both type 2 diabetes and vitamin D insufficiency include aging, obesity, low physical activity, and African-American ethnicity. Additionally, there are links between vitamin D insufficiency and conditions like osteoporosis, heart disease, and metabolic syndrome. T2DM and vitamin D insufficiency have been linked in several studies. Furthermore, recent research has indicated that vitamin D may contribute to glucose tolerance by influencing insulin sensitivity and secretion. The 25 (OH)D circulating concentration is substantially lower in T2DM sufferers than in healthy controls. Additionally, older men with vitamin D insufficiency secrete more insulin after consuming glucose, while vitamin D deficiency is more common in women with type 2 diabetes (Talaie et al., 2013).

Obesity, which is frequently linked to hypovitaminosis D, increases the prevalence of type 2 diabetes. Because vitamin D is effectively stored in body fat stores, where it is no longer accessible, a sizable percentage of obese people likely suffer from chronic vitamin D deficiency. Functional changes like increased PTH levels are also linked to vitamin D insufficiency in obese people. Because PTH and insulin promote the formation of vitamin D, acute insulin insufficiency in diabetes mellitus may reduce vitamin D production. It is commonly recognized that individuals with hyperparathyroidism are more likely to suffer from diabetes and insulin resistance. Therefore, several linked metabolic consequences may be responsible for the association between type 2 diabetes, hypovitaminosis D, and impaired insulin secretion.

Insulin resistance and β -cell failure are two important characteristics of type 2 diabetes mellitus that have frequently been linked to inflammatory causes. Type 2 diabetes has been linked to an increase in acute-phase proteins, cytokines, and mediators linked to endothelial dysfunction. Numerous markers of systemic inflammation, including plasminogen activator inhibitor-1, C-reactive protein, interleukin-6 (IL-6) and its receptor, and tumor necrosis factor (TNF)- α and TNF- β , have been reported to be abnormal in type 2 diabetes mellitus. Insulin resistance can be caused by a number of ways, including direct interference with insulin signaling by immune mediators such TNF- α and IL-6. Vitamin D has been demonstrated to have a variety of immune functions, including promoting monocyte differentiation into macrophages, which increases their cytotoxic activity; decreasing the antigen-presenting ability of macrophages to lymphocytes; preventing dendritic cell maturation; inhibiting T lymphocyte-mediated immunoglobulin synthesis in B cells; and preventing delayed-type hypersensitivity reactions (Palomer et al., 2008).

Triglycerides (TG), cholesterol (CHL), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) are among the lipid abnormalities that define hyperlipidemia (HL), commonly referred to as dyslipidemia, a common metabolic condition. Type 2 diabetes mellitus (T2DM) and obesity are common co-occurring conditions with hyperlipidemia. Lower serum 25(OH)D concentrations significantly increased the risk of hyperlipidemia, particularly the risk of total cholesterol and triglyceride abnormalities, and the prevalence of hyperlipidemia was considerably higher in those with vitamin D deficiency than in those with adequate vitamin D levels. A strong correlation exists between increased vulnerability to HL and decreased serum 25(OH)D levels. It also supports the idea that vitamin D regulates lipid metabolism in a complex way, affecting the pathophysiology of HL. Because it increases fatty acid oxidation and mitochondrial metabolism, vitamin D may increase energy consumption and lower lipid levels. It can also be stored in fat cells (Wang et al., 2024).

Recommendation

Healthcare organizations and individual healthcare providers from multiple disciplines (doctors, nurses, pharmacists, dieticians, and diabetes educators) must be given time and resources to collaborate as they educate and care for individual and groups of patients. This epidemic will require an urgent and unwavering commitment to aggressive solutions at national levels with public policies, public health funding, and economic incentives for local communities to start diabetes prevention programs including all the parameters involving in lowering blood glucose levels.

Conclusion

The incidence and prevalence of type 2 diabetes are significant causes of mortality in humans. Vitamin D insufficiency may be common among people with type 2 diabetes, and vitamin may impact how well these patients control their blood

sugar levels. People with low serum 25(OH)D concentrations are more likely to have hyperlipidemia, and they are also at a much-increased risk of abnormalities in total cholesterol and triglycerides.

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Conflict of Interest

It is declared that there is no conflict of interest among the Authors

References

- Abdul Basith Khan, M., Hashim, M. J., King, J. K., Govender, R. D., Mustafa, H., & Al Kaabi, J. (2020). Epidemiology of type 2 diabetes global burden of disease and forecasted trends. *Journal of epidemiology and global health*, 10(1), 107-111.
- Adnan, M., & Aasim, M. (2020). Prevalence of type 2 diabetes mellitus in adult population of Pakistan: a meta-analysis of prospective cross-sectional surveys. *Annals of global health*, 86(1), 7.
- Berridge, M. J. (2017). Vitamin D deficiency and diabetes. *Biochemical Journal*, 474(8), 1321-1332.
- Blair, M. (2016). Diabetes mellitus review. *Urologic nursing*, 36(1).
- Chatterjee, S., Khunti, K., & Davies, M. J. (2017). Type 2 diabetes. *The lancet*, 389(10085), 2239-2251.
- De Kort, S., Keszthelyi, D., & Masclee, A. A. M. (2011). Leaky gut and diabetes mellitus: what is the link?. *Obesity Reviews*, 12(6), 449-458.
- Deshmukh, C. D., Jain, A., & Nahata, B. (2015). Diabetes mellitus: a review. *Int. J. Pure Appl. Biosci*, 3(3), 224-230.
- Fiscaletti, M., Stewart, P., & Munns, C. F. (2017). The importance of vitamin D in maternal and child health: a global perspective. *Public health reviews*, 38, 1-17.
- Lee, C. J., Iyer, G., Liu, Y., Kalyani, R. R., Bamba, N. D., Ligon, C. B., ... & Mathioudakis, N. (2017). The effect of vitamin D supplementation on glucose metabolism in type 2 diabetes mellitus: A systematic review and meta-analysis of intervention studies. *Journal of Diabetes and its Complications*, 31(7), 1115-1126.
- Murdaca, G., & Gangemi, S. (2022). Vitamin D in health and disease. *Biomedicines*, 11(1), 10.
- Olokoba, A. B., Obateru, O. A., & Olokoba, L. B. (2012). Type 2 diabetes mellitus: a review of current trends. *Oman medical journal*, 27(4), 269.
- Palomer, X., González-Clemente, J. M., Blanco-Vaca, F., & Mauricio, D. (2008). Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism*, 10(3), 185-197.
- Saif-Elnasr, M., Ibrahim, I. M., & Alkady, M. M. (2017). Role of Vitamin D on glycemic control and oxidative stress in type 2 diabetes mellitus. *Journal of Research in Medical Sciences*, 22(1), 22.
- Solis-Herrera, C., Triplitt, C., Reasner, C., DeFronzo, R. A., & Cersosimo, E. (2015). Classification of diabetes mellitus
- Talaei, A., Mohamadi, M., & Adgi, Z. (2013). The effect of vitamin D on insulin resistance in patients with type 2 diabetes. *Diabetology & metabolic syndrome*, 5, 1-5
- Wang, J., Shi, T., Xu, L., Li, Y., Mi, W., Wang, C., ... & Hu, Z. (2024). Correlation between hyperlipidemia and serum vitamin D levels in an adult Chinese cohort. *Frontiers in Nutrition*, 11, 1302260.
- Wu, C., Qiu, S., Zhu, X., & Li, L. (2017). Vitamin D supplementation and glycemic control in type 2 diabetes patients: A systematic review and meta-analysis. *Metabolism*, 73, 67-76.
- Zia, A., Bhatti, A., Jalil, F., Wang, X., John, P., Kiani, A. K., ... & Kamboh, M. I. (2016). Prevalence of type 2 diabetes—associated complications in Pakistan. *International Journal of Diabetes in Developing Countries*, 36, 179-188.

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