THE ASSOCIATION BETWEEN VITAMIN D DEFICIENCY AND INSULIN RESISTANCE

Negmatova Gulzoda Shuhratovna *- PhD, Associate Professor, Head of the Department of Endocrinology*
Usmonov Azimbek *– Clinical Resident of the Department of Endocrinology*
Ibodullayev Avazbek *- Clinical Resident of the Department of Endocrinology*
Shodiyev Dilmurod *- Clinical Resident of the Department of Endocrinology*
Samarkand State Medical University
Samarkand, Uzbekistan

Abstract. Vitamin D deficiency is a widespread public health issue affecting over one billion people worldwide and has increasingly been linked to insulin resistance and type 2 diabetes mellitus. Vitamin D acts through the vitamin D receptor (VDR), which is expressed in pancreatic β-cells, skeletal muscle, adipose tissue, and the liver-tissues essential for glucose metabolism. Several mechanisms may explain this association, including impaired β-cell function and insulin secretion, disrupted calcium homeostasis, increased systemic inflammation, and altered expression of genes involved in insulin signalling. Epidemiological studies have consistently reported an inverse relationship between serum 25-hydroxyvitamin D levels and insulin resistance, commonly assessed using HOMA-IR. Although intervention trials have shown mixed findings, vitamin D supplementation appears to improve insulin sensitivity and glycaemic control in individuals with established deficiency. This review summarises current evidence on the relationship between vitamin D deficiency and insulin resistance and considers the potential role of vitamin D supplementation in prevention and management strategies.

Keywords: vitamin D deficiency, insulin resistance, 25-hydroxyvitamin D, HOMA-IR, pancreatic β-cell function, type 2 diabetes mellitus, vitamin D receptor, vitamin D supplementation, glucose metabolism, inflammation

Introduction

Vitamin D is a fat-soluble secosteroid with well-established roles in calcium and phosphate homeostasis, skeletal mineralisation, and immune regulation. In recent decades, however, attention has shifted considerably toward its extraskeletal functions, with epidemiological, mechanistic, and clinical data collectively implicating vitamin D deficiency in the pathogenesis of a range of non-skeletal conditions, including

cardiovascular disease, autoimmune disorders, and metabolic dysregulation. Among these, the association between vitamin D deficiency and insulin resistance has attracted particular scientific interest given the near-simultaneous global epidemics of hypovitaminosis D and type 2 diabetes mellitus (T2DM) [1,2].

Insulin resistance defined as a diminished biological response of target tissues to a given concentration of insulin is the central pathophysiological mechanism underlying T2DM, metabolic syndrome, and non-alcoholic fatty liver disease. It precedes overt hyperglycaemia by years and is detectable early in the natural history of glucose dysregulation. The identification of modifiable nutritional factors that contribute to insulin resistance is therefore of considerable clinical and public health importance, as it opens potential avenues for primary prevention. Vitamin D, whose deficiency affects an estimated one billion individuals globally, represents a particularly attractive candidate given its broad metabolic actions and the widespread availability of supplementation [2, 3].

Vitamin D metabolism and the vitamin D receptor

Vitamin D is obtained through cutaneous synthesis following ultraviolet B irradiation of 7-dehydrocholesterol in the skin and, to a lesser extent, through dietary intake. It undergoes sequential hepatic hydroxylation to 25-hydroxyvitamin D (25(OH)D) -the principal circulating form and the standard measure of vitamin D status -and subsequent renal and extrarenal hydroxylation to the biologically active metabolite 1,25-dihydroxyvitamin D (calcitriol), catalysed by 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1). Vitamin D deficiency is conventionally defined as a serum 25(OH)D concentration below 20 ng/mL (50 nmol/L), with insufficiency defined as 20–29 ng/mL [1, 4].

The metabolic actions of calcitriol are mediated primarily through the vitamin D receptor (VDR), a nuclear receptor that functions as a ligand-activated transcription factor, regulating the expression of hundreds of target genes through vitamin D response elements in their promoter regions. The VDR is expressed in virtually all nucleated cells, including pancreatic β-cells, skeletal muscle fibres, hepatocytes, and adipocytes -precisely the tissues that are central to insulin secretion and insulin-mediated glucose disposal. The expression of CYP27B1 in these same tissues indicates that local activation of vitamin D metabolites can modulate insulin signalling in an autocrine and paracrine fashion, independently of circulating calcitriol concentrations [3, 5].

Mechanisms linking vitamin D deficiency to insulin resistance

Vitamin D has been implicated in a range of non-skeletal disorders, particularly metabolic conditions such as metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), impaired fasting glucose (IFG), non-alcoholic fatty liver disease (NAFLD), and polycystic ovary syndrome (PCOS), all of which are closely associated with insulin

resistance (IR). Numerous studies have reported an inverse relationship between serum vitamin D levels and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), a widely used indicator of insulin resistance reflecting the compensatory increase in insulin secretion required to maintain normal glucose homeostasis [6]. Evidence also suggests that vitamin D supplementation may improve insulin sensitivity and reduce circulating insulin concentrations, particularly in individuals with low vitamin D status. Furthermore, the association between vitamin D deficiency and elevated HOMA-IR appears to become stronger with increasing body mass index (BMI) [3,6].

The proposed link between vitamin D deficiency and insulin resistance is supported by several molecular mechanisms. These include the regulation of insulin receptor expression, modulation of inflammatory cytokine production, and the activity of vitamin D receptor (VDR) polymorphisms in pancreatic β-cells. Vitamin D influences cellular function through both genomic and non-genomic pathways, affecting the transcription of genes involved in glucose metabolism and insulin signalling. Taken together, these findings suggest that vitamin D deficiency and insulin resistance may be closely interconnected at the genetic and molecular levels [2, 5].

Vitamin D may enhance insulin sensitivity through several molecular pathways. It has been shown to increase insulin receptor expression in skeletal muscle, liver, and adipose tissue, thereby improving cellular responsiveness to insulin. Moreover, vitamin D acts as an epigenetic regulator, influencing the transcription of genes involved in insulin signalling, including insulin receptor substrate (IRS), a key mediator of insulin action. Increased IRS expression has been associated with improved insulin sensitivity in target tissues. Vitamin D has also been reported to enhance glucose transport, increase insulin receptor responsiveness, and facilitate the conversion of proinsulin into insulin [7].

Vitamin D deficiency is linked to increased production of pro-inflammatory cytokines, which may contribute to insulin resistance, particularly in individuals with obesity. The high prevalence of hypovitaminosis D in obese populations has been attributed to reduced sun exposure, inadequate dietary intake, and sequestration of vitamin D within adipose tissue [42]. Additionally, dysregulated leptin secretion associated with excess abdominal fat has been implicated in the development of insulin resistance. Some evidence suggests that vitamin D supplementation may lower leptin concentrations and reduce body mass index (BMI), potentially through appetite-regulating mechanisms mediated by vitamin D receptors in the hypothalamus [2, 3].

The vitamin D receptor (VDR), a member of the nuclear receptor superfamily, functions as a transcription factor that mediates the biological effects of vitamin D by regulating the expression of hormone-responsive genes, including those involved in intracellular signalling pathways [40]. Vitamin D may influence pancreatic β-cell

function through both direct and indirect mechanisms. Directly, vitamin D binds to VDR expressed in β-cells, thereby supporting insulin secretion [42,46]. Indirectly, it regulates intracellular calcium homeostasis, a critical determinant of insulin release, as calcium-dependent signalling plays a central role in β-cell function [46]. Altered calcium metabolism in insulin-sensitive tissues such as skeletal muscle and adipose tissue may therefore contribute to the development of insulin resistance. Furthermore, recent evidence suggests that deletion or dysfunction of VDR in macrophages promotes insulin resistance, highlighting the importance of VDR-mediated pathways in glucose metabolism and metabolic homeostasi [5, 7].

Recent studies have demonstrated that 1-α-hydroxylase, the enzyme responsible for activating vitamin D, is expressed in pancreatic β-cells, further supporting a role for vitamin D in glucose homeostasis [11]. Beyond its genomic actions, vitamin D exerts non-genomic effects through the activation of multiple intracellular signalling pathways, including phosphatidylinositol-3 kinase (PI3K), phospholipase C (PLC), protein kinase A (PKA), protein kinase C (PKC), mitogen-activated protein kinases (MAPKs), and calcium-dependent kinases [7,8]. These pathways interact with vitamin D response elements (VDREs) and regulate the expression of vitamin D-responsive genes.

In addition, vitamin D can modulate cellular activity through protein–protein interactions involving the vitamin D receptor (VDR). This alternative non-genomic mechanism influences several transcription factors and signalling molecules, including IKKβ, STAT1, RunX1, c-Jun, β-catenin, and CREB, thereby affecting the expression of genes involved in immune regulation, antiviral responses, inflammation, and cell survival [11]. These actions may contribute to the broader metabolic and immunomodulatory effects of vitamin D.

Epidemiological evidence

Cross-sectional and prospective epidemiological studies have consistently demonstrated an inverse association between circulating 25(OH)D concentrations and indices of insulin resistance. A systematic review and meta-analysis published in Scientific Reports in 2023, incorporating data from multiple populations, confirmed a significant inverse correlation between serum and supplemental vitamin D levels and HOMA-IR scores in patients with T2DM, with higher vitamin D concentrations associated with lower insulin resistance indices across diverse demographic groups [6].

A case-control study published in 2025, evaluating 140 participants -70 T2DM patients and 70 age- and sex-matched healthy controls -found that serum 25(OH)D levels were significantly lower and HOMA-IR scores significantly higher in T2DM patients compared with controls, with an inverse correlation observed between vitamin D levels and insulin resistance. Logistic regression analysis confirmed that vitamin D deficiency was independently associated with higher insulin resistance after adjustment

for confounders including age, body mass index, and glycaemic control, providing additional clinical evidence that vitamin D status is a meaningful determinant of insulin sensitivity in patients with established T2DM [8].

A systematic review published in Cureus in 2024 evaluating the effect of vitamin D supplementation on T2DM risk found that lower vitamin D levels were associated with a 24% increased risk of developing T2DM for each 25 nmol/L decrease in 25(OH)D, further supporting the hypothesis that adequate vitamin D status may confer protection against the development of insulin resistance and overt T2DM [9].

Interventional evidence: Vitamin D supplementation

Randomised controlled trials examining the effect of vitamin D supplementation on insulin resistance have yielded heterogeneous results, with the magnitude and consistency of benefit appearing to depend critically on baseline vitamin D status, supplementation dose, duration of treatment, and the degree of insulin resistance at enrolment. A systematic review and meta-analysis published in 2023, which reviewed evidence from 33 eligible studies on the impact of vitamin D deficiency on T2DM outcomes, found that supplementation in vitamin D-deficient T2DM patients was associated with significant reductions in fasting plasma glucose, HbA1c, and HOMA-IR, particularly when baseline 25(OH)D concentrations were below 20 ng/mL [1].

A 2025 review published in Recent Progress in Nutrition summarising clinical and mechanistic evidence reported that supplementation with 2,000 IU/day of vitamin D3 for 12 weeks in T2DM patients with documented vitamin D deficiency resulted in significant reductions in fasting plasma glucose and HbA1c, while higher-dose supplementation (4,000 IU/day) in individuals with prediabetes was associated with an increased rate of reversion to normoglycaemia and a reduced risk of progression to T2DM [5].

Conversely, several well-designed trials conducted in populations with near-normal baseline vitamin D status, including the VITAL and D-HEALTH trials, have not demonstrated significant improvements in insulin sensitivity or diabetes incidence with supplementation, suggesting that the benefit of vitamin D repletion may be restricted to individuals with genuine deficiency. These findings highlight the importance of baseline vitamin D measurement and targeted supplementation strategies, as well as the need for further large-scale trials designed specifically around populations with confirmed hypovitaminosis D [4, 10].

Clinical implications and Mmanagement

The available evidence supports routine assessment of vitamin D status in patients with insulin resistance, prediabetes, or T2DM, particularly in geographic regions with limited sunlight exposure and in populations with established risk factors for vitamin D deficiency, including obesity, dark skin pigmentation, limited outdoor activity, and exclusive indoor dwelling. Correction of vitamin D deficiency through appropriate

supplementation is a safe, inexpensive, and widely accessible intervention that may contribute to improved insulin sensitivity, particularly in deficient patients with early or established glucose dysregulation [10,11].

Updated clinical practice guidelines from the Endocrine Society published in 2024 provide evidence-based recommendations on vitamin D supplementation for the prevention of disease, with specific guidance on target serum concentrations, supplementation doses, and monitoring intervals in populations at metabolic risk, including those with obesity and T2DM. These guidelines endorse targeted supplementation in individuals with documented deficiency while acknowledging the current limitations of the evidence base for universal supplementation in those with normal vitamin D status [10].

Conclusion

The association between vitamin D deficiency and insulin resistance is supported by a convergent body of mechanistic, epidemiological, and interventional evidence. Vitamin D influences insulin sensitivity through multiple pathways -including direct effects on β-cell function and insulin gene transcription, regulation of intracellular calcium homeostasis, suppression of pro-inflammatory signalling, and transcriptional control of glucose transporter expression -all of which are impaired when vitamin D status is inadequate. Epidemiological data consistently demonstrate an inverse relationship between 25(OH)D concentrations and HOMA-IR, and interventional studies suggest that supplementation in vitamin D-deficient individuals can meaningfully improve glycaemic parameters and reduce insulin resistance indices. Given the global prevalence of both vitamin D deficiency and T2DM, routine screening for vitamin D status and targeted supplementation in at-risk populations represent clinically practical and evidence-supported strategies for addressing a modifiable contributor to insulin resistance and metabolic disease.

References:

1. Taderegew M.M., Woldeamanuel G.G., Wondie A., et al. Vitamin D deficiency and insufficiency on the outcome of type 2 diabetes mellitus patients: a systematic review. Nutrients. 2023;15(10):2373.

2. Berridge M.J. Vitamin D deficiency and diabetes. Biochemical Journal. 2021;478(6):1321–1332.

3. Szymczak-Pajor I., Śliwińska A. Analysis of association between vitamin D deficiency and insulin resistance. Nutrients. 2019;11(4):794.

4. Endocrine Society. Vitamin D for the prevention of disease: an Endocrine Society clinical practice guideline. Journal of Clinical Endocrinology & Metabolism. 2024;109(7):1907–1947.

5. Sharma S., Karhana S., Khan M.A. The impact of vitamin D on type 2 diabetes

mellitus: exploring its role in glucose metabolism and insulin sensitivity. Recent Progress in Nutrition. 2025;5(3):021.

6. Lei X., Zhou Q., Wang Y., Fu S., Li Z., Chen Q. Serum and supplemental vitamin D levels and insulin resistance in T2DM populations: a meta-analysis and systematic review. Scientific Reports. 2023;13(1):12343.

7. Alkharfy K.M., Al-Daghri N.M., Yakout S.M., et al. Vitamin D supplementation improves insulin sensitivity and dyslipidaemia in subjects with type 2 diabetes mellitus and metabolic syndrome. Scientific Reports. 2021;11(1):9783.

8. Jain P.K., Nigotia P., Mishra A., Singh L.P. Association of vitamin D deficiency with insulin resistance among type 2 diabetes mellitus patients: a case-control study. Bioinformation. 2025;21(2):897–903.

9. Evaluating the effect of vitamin D supplementation on type 2 diabetes risk: a systematic review. Cureus. 2024.

10. Pittas A.G., Kawahara T., Jorde R., et al. Vitamin D supplementation and prevention of type 2 diabetes. New England Journal of Medicine. 2023;389(21):1993–2003.

11. Argano, C.; Mirarchi, L.; Amodeo, S.; Orlando, V.; Torres, A.; Corrao, S. The Role of Vitamin D and Its Molecular Bases in Insulin Resistance, Diabetes, Metabolic Syndrome, and Cardiovascular Disease: State of the Art. Int. J. Mol. Sci. 2023, 24, 15485