VITAMIN D RECEPTOR CDX2 POLYMORPHISM IN NON-INSULIN DEPENDENT DIABETIC PATIENTS; REVIEW ARTICLE

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Abstract
T2DM is a disease of multifactorial etiologies caused by insulin resistance and impaired insulin secretion. Increasing evidence indicates that genetic factors contribute to T2DM susceptibility. Evidence from various studies suggest that vitamin D receptor (VDR) gene polymorphisms are associated with type 2 diabetes (T2D); However, these results have been disputable. **Aim**; in this article we aimed to present Vitamin D receptor Cdx2 polymorphism in non-insulin dependent diabetic patients, **Methods**: We performed a search of MEDLINE through PubMed and Web of Science [Science Citation Index Expanded, SCI-EXPANDED), Social Sciences Citation Index (SSCI), and Emerging Sources Citation Index (ESCI)] of all scientific literature published from May 2020 until April 2023, **Summary**; Numerous studies disclosed the independent role of VDR genetic polymorphisms involved in pathogenesies of various metabolic disorders like type 2 diabetes mellitus in different populations, Such interlationshipis involvedcomplex inheritance pattern.The polymorphisms of various genes including vitamin D receptor (VDR) might affect genetic susceptibility of T2DM by developing malfunctioning of beta pancreatic cells or insulin resistance. Geneticarchitecture of T2DM is different among various ethnic populations.

keywords: vitamin D receptor; genetic polymorphism; type 2 diabetes mellitus

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Diabetes mellitus (DM)
DM is a chronic metabolic disease of the endocrine system characterized by hyperglycemia, and dysregulation of lipid and protein metabolism, connected with an absolute or relative defect in insulin secretion or insulin activity with environmental and genetic factors **(1).**

Epidemiology: diabetes continues to be a public health problem with a significant burden on the Egyptian economy. Patients with type 2 diabetes (T2D) constitute approximately 90%-95% of all patients with diabetes worldwide and represent a growing epidemic. In 2013, 382 million adults diagnosed with diabetes worldwide. This number expected to grow to 592 million in 2035. The International Diabetes Federation (IDF) listed Egypt among the world top 10 countries in the number of patients with diabetes. In Egypt, the prevalence of diabetes is around 15.56% among adults between 20 and 79 years of age, with an annual death of 86,478 related to diabetes.

Risk factors of T2DM: T2DM influenced by a combination of genetic and metabolic variables. Ethnicity, family history, prior gestational diabetes, and advanced age are non-modifiable variables; however, modifiable factors such as obesity, poor food, low physical activity level, and smoking can all contribute to the development of T2DM **(2).**

Regarding the pathophysiology of T2DM: A malfunctioning between insulin action and insulin secretion results in abnormally high glucose levels in the blood. In the case of β-cell dysfunction, insulin secretion is reduced, impairing the body to maintain physiological glucose levels. On the other hand, insulin resistance contributes to increased glucose production in the liver and decreased glucose uptake both in the muscle and adipose tissue. when both β-cell dysfunction and insulin resistance are present, hyperglycemia is increased leading to the progression of T2DM **(3).**

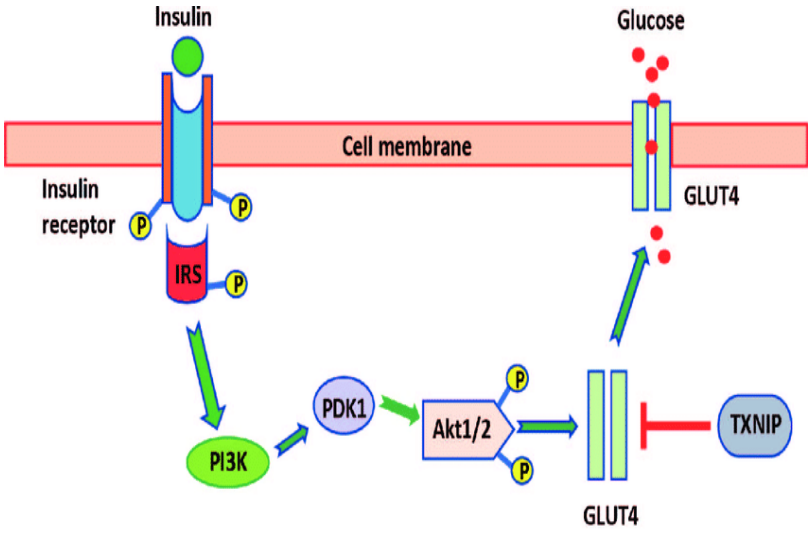

Figure (1): insulin signaling pathway **(4)**

Insulin Resistance: IR refers to a decrease in the metabolic response of insulin-responsive cells to insulin. There are three categories of IR: (1) diminished insulin secretion by β-cells (2) insulin antagonists in the plasma that impair insulin receptors or signaling; and (3) impaired insulin response in target tissues. The action of insulin is affected by growth hormone and insulin-like growth factor 1 (IGF-1) in the fed state. While fasting, the insulin response affected by glucagon, glucocorticoids, and catecholamines to prevent insulin-induced hypoglycemia.

Complications of diabetes mellitus: T2DM characterized by high prevalence and progressive development of both macrovascular complications (cardiovascular diseases (CVD)) and microvascular complications (diabetic kidney disease (DKD), diabetic retinopathy, and neuropathy) which are the leading cause of morbidity and mortality in individuals with diabetes **(5).**

1- Acute Diabetic Complications: Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are the two most common life-threatening acute metabolic complications of DM **(6).**

2- Chronic Diabetic Complications: Chronic diabetic complications (vascular complications) categorized as either those affecting large vessels (macrovascular complications) or those affecting micro vessels (microvascular complications). Microvascular complications include diabetic retinopathy (DR), diabetic nephropathy (DN), and diabetic peripheral neuropathy (DPN), whereas macrovascular complications include coronary artery disease (CAD) (cardiovascular disease) and peripheral artery disease (PAD) **(7).**

Diagnosis of T2DM:

1) History and Physical: Diabetic patients most commonly present with increased thirst, increased urination, lack of energy and fatigue, bacterial and fungal infections, and delayed wound healing. Others may complain of numbness, tingling in hands or feet, or blurred vision **(8).**

If there is no clearly defined clinical diagnosis, the same test should be repeated with a new blood sample immediately.

The diagnosis is verified if the same test yields the same findings **(9)**

Treatment of Pre-Diabetes:

Pre-diabetes is a reversible condition. If proper measures are taken during this critical period, then a person can be spared long-term complications. Pre-diabetes is the early indicator of diabetes that occurs when the patient is diagnosed with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). The onset of both pre-diabetes and diabetes begins with the insulin resistance of cells **(10).**

1) Lifestyle Intervention: Treatment of pre-diabetes through lifestyle intervention targets the risk factors such as obesity and diet. Lifestyle intervention mainly comprises regular and nutritious dietary advice, instructions for physical activities, and weight loss **(11).**

2) Pharmacological Interventions: If adequate glycemia cannot be achieved, metformin is the first line of therapy. Following metformin many other therapies such as oral sulfonylureas, and dipeptidyl peptidase-4 (DPP-4) inhibitors. GLP-I receptor agonists, SGLT-2 inhibitors, pioglitazone especially if the patient has fatty liver disease, alpha-glucosidase inhibitors, and insulin are available.

Vitamin D

Vitamin D (also referred to as "calciferol") is a fat-soluble vitamin that is naturally present in a few foods, added to others, and available as a dietary supplement. It also produced endogenously when ultraviolet (UV) rays from sunlight strike the skin and trigger vitamin D synthesis **(12).**

Sources of Vitamin D:

1) Sun exposure: Most people in the world meet at least some of their vitamin D needs through exposure to sunlight. Type B ultraviolet (UVB) radiation with a wavelength of approximately 290–320 nanometers penetrates uncovered skin and converts cutaneous 7-dehydrocholesterol to pro-vitamin D3, which in turn becomes vitamin D3.

2) Food: Few foods naturally contain vitamin D. The flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources. liver, cheese, and egg yolks have small amounts of vitamin D, primarily in the form of vitamin D3 and its metabolite 25(OH) D3. Mushrooms provide variable amounts of vitamin D2 **(13).**

3) Dietary supplement: Dietary supplements can contain vitamins D2 or D3. In addition, most steps in the metabolism and actions of vitamins D2 and D3 are identical.

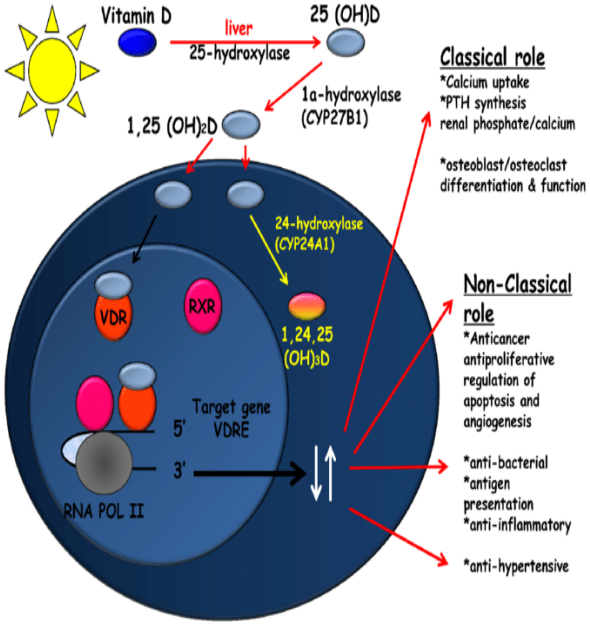

Figure (2): Mechanism of action of vitamin D **(14)**

Vitamin D as a hormone: Calcitriol [1,25-dihydroxycholecalciferol ($1,25(OH)_2D$)], an active hormonal form of vitamin D, due to its action belongs to a broad group of hormones (steroid hormones), being transcription factors of genes for the target proteins, being synthesis in the body, biological action of calcitriol is mediated by the intracellular, highly specific vitamin D receptor (VDR) **(15).**

Actions of vitamin D:

1) Classical Actions of Vitamin D: The classical role of $1,25(OH)_2$ D in calcium/bone metabolism, is by regulation of intestinal calcium absorption, renal calcium reabsorption, and mobilization of calcium and phosphate from bone **(16).**

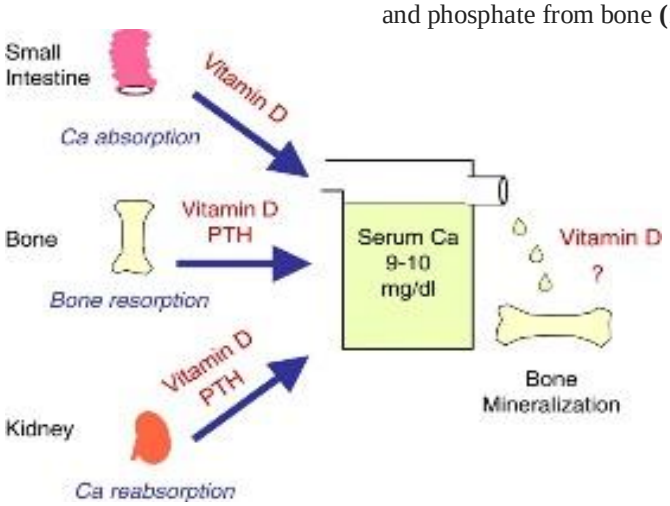

Figure (3): Classical action of vitamin D to maintain serum calcium homeostasis **(17).**

2) Novel Actions of Vitamin D: Vitamin D regulates cell proliferation and differentiation and has a key role in the responses of the immune and nervous systems. In fact, observational studies suggest that high serum concentrations of vitamin D protect against cardiovascular disease (CVD), diabetes, and colorectal cancer **(18).**

Evidence of extraskeletal effects of 1, 25$(OH)_2$ D3 includes xenobiotic detoxification, oxidative stress reduction, neuroprotective functions, antimicrobial defense, immunoregulation, anti-inflammatory/ anticancer actions, antiaging and cardiovascular benefits **(19).**

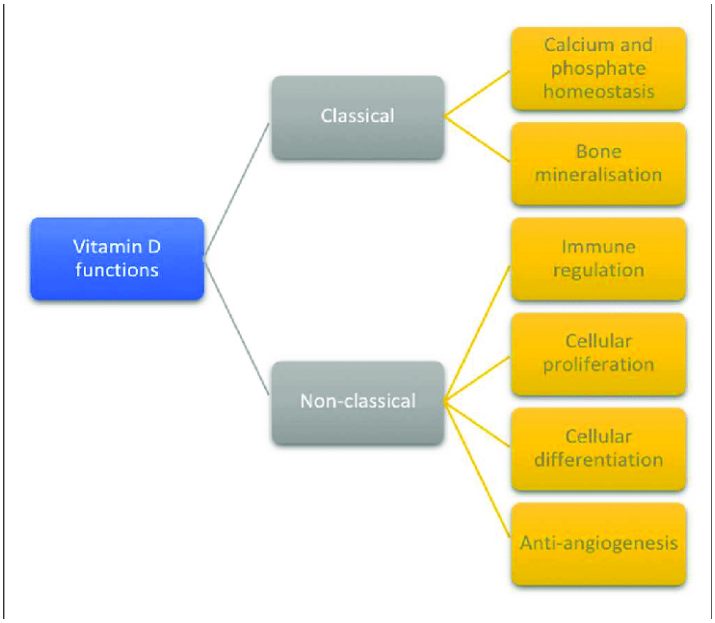

Figure (4): Classical and non- classical functions of vitamin D **(20)**

Vitamin D3 and diabetes mellitus: There is strong evidence suggesting that normal levels of vitD3 are associated with normal insulin sensitivity and glucose homeostasis. This evidence suggests that vitD3 is involved in the pathophysiology of insulin resistance and DM **(21).**

1. VitD3 and beta-cell function: There is evidence suggesting that calcitriol preserves beta-cell mass and improves islets' function. As the insulin secretion process is a calcium-dependent mechanism, it has been suggested that the active form of vitD3 in plasma is correlated to normal insulin release by the beta cells.

2. VitD3 and insulin secretion: Insulin secretion depends on a number of factors, including calcium. Vitamin D affects the function of the protein calbindin and acts as a modulator of depolarization-stimulated insulin release by re-distributing intracellular calcium **(22).**

3.VitD3 and peripheral insulin sensitivity: vitamin D increases insulin sensitivity that might be mediated via binding of 1,25$(OH)_2D_3$ to VDR in insulin-responsive cells. 1,25$(OH)_2$D interacts with VDR which in turn binds to retinoid X receptor (RXR). This data confirms that vitamin D deficiency seems to be engaged in the onset of insulin resistance due to the down-expression of IR **(23).**

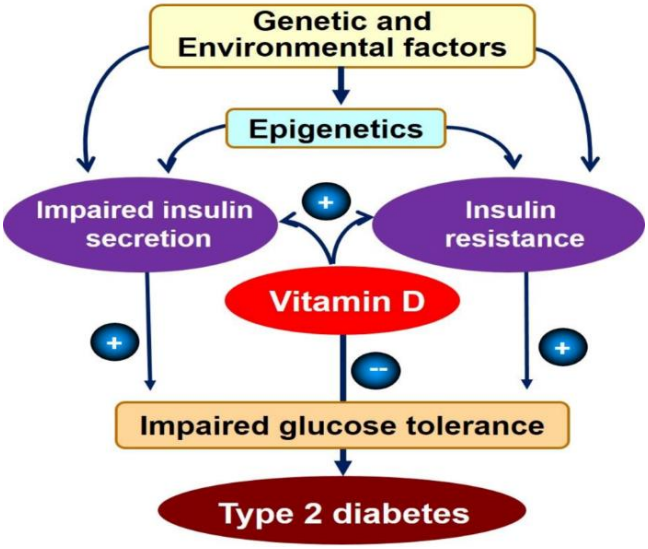

Figure (5): Association of vitamin D with insulin resistance and type 2 diabetes. **(24)**

Assessment of Vitamin D:

Current guidelines recommend using the serum circulating 25-OHD level to evaluate vitamin D status in patients who are at risk for vitamin D deficiency. 25-OHD is the most abundant vitamin D metabolite in circulation and is considered the best indicator of vitamin D status. There is solid evidence that serum 25-OHD is associated with clinical outcomes, such as bone mineralization, fracture risk, falls risk, all-cause mortality, and cardiovascular events **(25).**

The analysis elaborated by the Institute of Medicine (IOM) for recommendations for Vitamin D adequacy indicated a value <30 nmol/L **(<12 ng/mL)** as associated with vitamin D deficiency, leading to rickets in infants and children and to osteomalacia in adults. A level of 30 ≤ 50 nmol/L **(12≤20 ng/mL)** was considered inadequate for bone and overall health in healthy individuals and ≥50 nmol/L **(≥20 ng/mL)** was considered adequate for bone and overall health in healthy subjects **(26).**

The FOKI polymorphism

The FOKI is a polymorphic site in the VDR gene with a thymine (T) to cytosine (C) substitution in the start codon ATG (methionine), affecting the structure and the function of the encoded protein. The allelic variants of the FOKI polymorphism code result in two structurally different VDR proteins: the wild-type 424 amino acids (F allele, C) and the 427 amino acids (f allele, T) protein **(27).**

The FOKI polymorphism results in a protein shortened by three amino acids. These genetic variants have been associated with a predisposition to chronic diseases such as type 2 diabetes, cancer, autoimmune diseases, cardiovascular alterations, rheumatic arthritis, and metabolic bone diseases **(28).**

The Cdx2 polymorphism

The caudal-type homeobox protein 2 (Cdx2) polymorphism would be important among VDR polymorphisms because it is located in the promoter region of the VDR gene **(29).**

Cdx2 polymorphism (rs11568820) is a guanine (G) to adenine (A) sequence variation in the promoter area (1e promoter) of the VDR gene, more specifically in a binding site for an intestinal-specific transcription factor which is called Cdx2. It was first found among Japanese women, but it has since been shown to be present also among Caucasians as well as other race groups **(30).**

Obesity

Obesity is classified as overweight or obese (defined by a body mass index ≥ 25 or 30 kg/m^2, respectively) **(4).**

The body mass index (BMI) is a simple index to classify overweight and obesity in adults and defined as weight in kg/height in m^2. Individuals with a BMI ≥30 kg/m^2 considered obese, and individuals with a BMI between 25 and 29.9 kg/m^2 considered overweight **(31).**

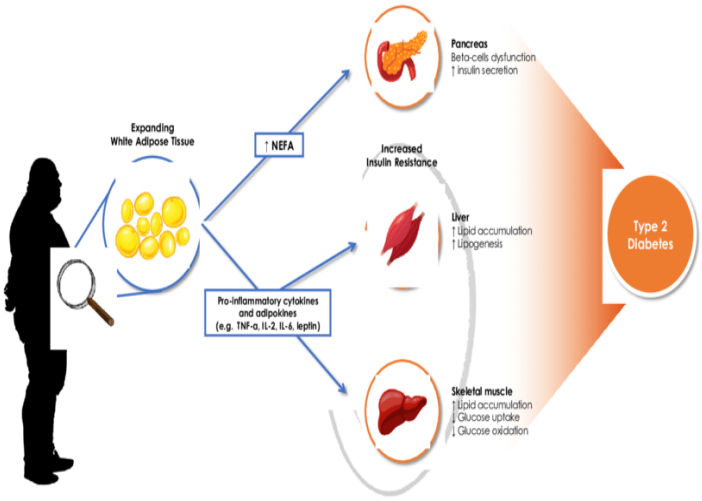

Figure (6): Mechanistic links between obesity and type 2 diabetes **(32)**

Obesity and vitamin D deficiency: The association between VD deficiency and obesity has been confirmed by numerous studies, but the presence of a causal relationship is still unclear **(33).** A study showed that 1,25(OH)2D3 inhibits lipolysis in human adipocytes, possibly via increased intracellular calcium levels resulting in decreased cAMP levels and a reduced hormone-sensitive lipase (HSL) phosphorylation. In contrast, recent data showed that 1,25(OH)2D3 increased glycerol release in adipocytes.

REFERENCES

1. **Bijelic, R, Balaban, J, Milicevic, S. (2020).** The Association of Obesity and Microvascular Complications with Glycemic Control in Patients with Type 2 Diabetes Mellitus. *Medical Archives*, *74*(1), 14. doi: 10.5455/medarh.2020.74.14-18.

2. **Fan, W. (2017).** Epidemiology in diabetes mellitus and cardiovascular disease. *Cardiovascular endocrinology*, *6*(1), 8.
3. **Galicia-Garcia, U, Benito-Vicente, A, Jebari, S. (2020).** Pathophysiology of type 2 diabetes mellitus. International journal of molecular sciences, 21(17), 6275.
4. **Chait, A, Den Hartigh, L. J. (2020).** Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. *Frontiers in cardiovascular medicine*, *7*, 22.
5. **Cole, J. B, Florez, J. C. (2020).** Genetics of diabetes mellitus and diabetes complications. *Nature reviews nephrology*, *16*(7), 377-390.
6. **Negera, G. Z, Weldegebriel, B, Fekadu, G. (2020).** Acute complications of diabetes and its predictors among adult diabetic patients at Jimma medical center, Southwest Ethiopia. *Diabetes, metabolic syndrome and obesity: targets and therapy*, *13*, 1237.
7. **Mauricio, D, Alonso, N, Gratacòs, M. (2020).** Chronic Diabetes Complications: The Need to Move beyond Classical Concepts. *Trends In Endocrinology &Amp; Metabolism*, *31*(4), 287-295. doi: 10.1016/j.tem.2020.01.007.
8. **Kempegowda, P, Chandan, J, Abdulrahman, S. (2019).** Managing hypertension in people of African origin with diabetes: Evaluation of adherence to NICE Guidelines. *Primary Care Diabetes*, *13*(3), 266-271. doi: 10.1016/j.pcd.2018.12.007.
9. **American Diabetes Association (2021).** 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care, 44(Suppl 1): S15-S33. doi:10.2337/dc21-S002.
10. **Kanat, M, DeFronzo, R. A, Abdul-Ghani, M. A. (2015).** Treatment of prediabetes. *World journal of diabetes*, *6*(12), 1207.
11. **Glechner, A, Keuchel, L, Affengruber, L. (2018).** Effects of lifestyle changes on adults with prediabetes: A systematic review and meta-analysis. *Primary Care Diabetes*, *12*(5), 393-408. doi: 10.1016/j.pcd.2018.07.003.
12. **Antonucci, R, Locci, C, Clemente, M. (2018).** Vitamin D deficiency in childhood: old lessons and current challenges. *Journal Of Pediatric Endocrinology And Metabolism*, *31*(3), 247-260. doi: 10.1515/jpem-2017-0391.
13. **Roseland, J. M, Phillips, K. M, Patterson, K. Y. (2018).** Vitamin D in foods: An evolution of knowledge. In *Vitamin D* (pp. 41-77). Academic Press.
14. **Shin, M. Y, Kwun, I. S. (2016).** Vitamin D: Hormone-like nutrient. *Journal of Nutrition and Health*, *49*(1), 1-7.
15. **Rusińska, A, Płudowski, P, Walczak, M. (2018).** Vitamin D supplementation guidelines for general population and groups at risk of vitamin D deficiency in Poland—recommendations of the polish Society of Pediatric Endocrinology and Diabetes and the expert panel with participation of national specialist consultants and representatives of scientific societies—2018 update. *Frontiers in Endocrinology*, *9*, 246.
16. **Saponaro, F, Saba, A, Zucchi, R. (2020).** An update on vitamin D metabolism. *International journal of molecular sciences*, *21*(18), 6573.
17. **Takahashi, N, Udagawa, N, Suda, T. (2014).** Vitamin D endocrine system and osteoclasts. *BoneKEy reports*, *3*.
18. **Carlberg, C. (2016).** Molecular approaches for optimizing vitamin D supplementation. *Vitamins & Hormones*, *100*, 255-271.
19. **Christakos, S, Dhawan, P, Verstuyf, A. (2016).** Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. *Physiological reviews*, *96*(1), 365-408.
20. **Soto, J. R, Anthias, C, Madrigal, A, Snowden, J. A. (2020).** Insights into the role of vitamin D as a biomarker in stem cell transplantation. *Frontiers in immunology*, *11*, 966.
21. **Maddaloni, E, Cavallari, I, Napoli, N. (2018).** Vitamin D and diabetes mellitus. *Vitamin D in Clinical Medicine*, *50*, 161-176.
22. **Zakharova, I, Klimov, L, Kuryaninova, V. (2019).** Vitamin D insufficiency in overweight and obese children and adolescents. *Frontiers in endocrinology*, *10*, 103.
23. **Szymczak-Pajor, I, Śliwińska, A. (2019).** Analysis of association between vitamin D deficiency and insulin resistance. *Nutrients*, *11*(4), 794.
24. **Wimalawansa, S. J. (2018).** Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. *The Journal of steroid biochemistry and molecular biology*, *175*, 177-189.
25. **Herrmann, M, Sullivan, D. R, Veillard, A. S. (2015).** Serum 25-hydroxyvitamin D: a predictor of macrovascular and microvascular complications in patients with type 2 diabetes. *Diabetes care*, *38*(3), 521-528.
26. **Ross, A. C, Taylor, C. L, Yaktine, A. L. (2011).** Committee to review dietary reference intakes for vitamin D and calcium. *Food and Nutrition Board*.
27. **Mohamed, S. A, Shipl, W. M, Sarhan, O. H. M. (2020).** The association between vitamin D receptor gene polymorphism (FoKI), type 2 diabetes, and microvascular/macrovascular complications in postmenopausal women. *Al-Azhar Assiut Medical Journal*, *18*(3), 330.
28. **Usategui-Martín, R, De Luis-Román, D. A, Fernández-Gómez, J. M. (2022).** Vitamin D receptor (VDR) gene polymorphisms modify the

response to Vitamin D supplementation: a systematic review and meta-analysis. *Nutrients*, *14*(2), 360.

29. **Oono, F, Sakamoto, Y, Tachi, Y. (2020).** Effect of Cdx2 polymorphism on the relationship between dietary calcium intake and peak bone mass in young Japanese women. *Nutrients*, *12*(1), 191.
30. **Köstner, K. I. M, Denzer, N, Mueller, C. S. (2009).** The relevance of vitamin D receptor (VDR) gene polymorphisms for cancer: a review of the literature. *Anticancer research*, *29*(9), 3511-3536.
31. **Okati-Aliabad, H, Ansari-Moghaddam, A, Kargar, S, Jabbari, N. (2022).** Prevalence of Obesity and Overweight among Adults in the Middle East Countries from 2000 to 2020: A Systematic Review and Meta-Analysis. *Journal of Obesity*, *2022*.
32. **Hwalla, N, Jaafar, Z, Sawaya, S. (2021).** Dietary management of type 2 diabetes in the MENA region: A review of the evidence. *Nutrients*, *13*(4), 1060.
33. **Vranić, L, Mikolašević, I, Milić, S. (2019).** Vitamin D deficiency: consequence or cause of obesity?. *Medicina*, *55*(9), 541.