



Effect of Vitamin D on Glucose Homeostasis and Insulin Sensitivity and Resistance in Type 2 Diabetes: A Systematic Review

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Abstract

Context: In recent years, non-bone diseases have been shown associated with vitamin D deficiency, of which type 2 diabetes is a group of metabolic disorders caused by insulin deficiency. Vitamin D deficiency affects the metabolic function of the cells, including beta-pancreatic cells. Regarding the effectiveness of vitamin D to control type 2 diabetes, the present study aimed at reviewing the relationship between vitamin D, glucose homeostasis, and insulin resistance in type 2 diabetes.

Evidence Acquisition: In this review, descriptive and analytic studies were analyzed using biochemical tests, questionnaires, and interviews. Using the keywords, such as vitamin D, type 2 diabetes, and insulin resistance, 11 articles, including descriptive-analytic, cross-sectional, case-control and interventional studies published from 1986 to 2018 were included.

Results: The levels of 25-hydroxyvitamin D in diabetics, women, and obese people are lower than others, which can indicate the effect of vitamin D on glucose homeostasis. In addition, vitamin D affects intracellular calcium, and, consequently insulin secretion. It can be said that vitamin D deficiency can make calcium unable to regulate insulin secretion.

Conclusions: According to the studies, it can be concluded that vitamin D can be effective to prevent and control type 2 diabetes. Also, there is no association between vitamin D and insulin secreted by food and hemoglobin A1c.

Keywords: Vitamin D Deficiencies, Diabetes Mellitus Type 2, Insulin Secretion, Insulin Resistance

1. Context

Diabetes mellitus is a chronic disorder in the pancreatic gland, which increases glucose levels due to low levels of insulin secretion or deficient action of insulin in the body (1). Type 2 diabetes leads to a reduction in insulin sensitivity and poor action of the pancreatic beta cells (2). The disruption of insulin activity causes fat, protein, and carbohydrates metabolism disorders (3).

Vitamin D has a great impact on chronic diseases, such as diabetes, which has been recently considered (4). Vitamin D deficiency can frequently be seen in women (5). Due to the type of clothing in women in the Middle East, vitamin D deficiency in these areas is more severe than Europe and the United States (6). Since vitamin D is a fat-soluble vitamin and can be surrounded by fat molecules, overweight people are more likely to have vitamin D deficiency (7). It is associated with atherosclerosis, depression, cancer, infectious and inflammatory bowel diseases, migraine, and

multiple sclerosis (8).

Vitamin D deficiency and diabetes are both endemic diseases (4) and also can be linked to osteoporosis and metabolic syndromes (5). Common risk factors among them are the African American race, obesity, aging, and reduced physical activity (5). Also, old men with vitamin D deficiency release more insulin following absorption of the glucose (5). Recently, researchers have found that serum levels of 25-hydroxyvitamin D are preventative factors for long-term diabetes complications, including cardiovascular and renal diseases (9). Therefore, it can be concluded that diabetic patients with liver and/or renal diseases have a lower vitamin D deficiency (4). It has been observed that 25-hydroxyvitamin D is decreased in type 2 diabetes, gestational diabetes, and obesity. It has also been shown that insulinogenic indices have improved with vitamin D supplementation (5).

On the other hand, the role of vitamin D on systemic inflammation has been identified. Systemic inflammation

has been shown associated with insulin resistance (10), which can be concluded that it is also linked to type 2 diabetes (10). Systemic inflammation of cytokines causes apoptosis in pancreatic beta cells (10). Vitamin D can improve the survival of beta cells by modulating the effects of cytokines (10). It also has an anti-inflammatory effect, by which can reduce insulin resistance.

1.1. Calcium, Vitamin D and Diabetes

Calcium indirectly affects insulin secretion. Accordingly, vitamin D can maintain extracellular calcium density at a normal level and keep calcium flux within the cell membrane at the natural level (4). Regarding the effect of vitamin D deficiency on intracellular calcium, by an increase in intracellular calcium, the insulin function is impaired after binding to its receptor, such as dephosphorylation of the glycogen synthase and adjustable glucose signal transduction (glucose transporter type 4) (11).

Since insulin secretion from pancreatic β cells is associated with the amount of intracellular calcium, and the elevated intracellular calcium inhibits insulin receptors, therefore, the lack of vitamin D can increase the parathyroid hormone levels and consequently, elevated intracellular calcium can inhibit insulin receptors (12). An acute increase in intracellular calcium makes insulin target cells unable to measure intracellular calcium flux for insulin performance (11). Increased intracellular calcium can weaken pancreatic β cells (11). This effect of vitamin D deficiency has not been explicitly discussed (11). The level of vitamin D is not correlated with basal insulin resistance in blood, however, it significantly stimulates insulin secretion following glucose intake (13).

In general, it can be concluded that calcium is unable to affect insulin secretion due to vitamin D deficiency (4). In summary, vitamin D has shown some improvements in diabetic cases, such as stimulating the expression of insulin receptor as a result of increased insulin activity, indirect effect on calcium due to improved insulin secretion, and an improvement in the responsiveness of the cells to transfer glucose into them (4).

1.2. Statement of the Problem

Diabetes mellitus is one of the leading causes of death worldwide (14). The prevalence of type 2 diabetes is growing at an alarming rate. Every year, more than a million people are diagnosed as new cases of diabetes in the United States (10). According to the World Health Organization (WHO), the number of diabetics has risen from 108 million in 1980 to 422 million in 2014, with 1.5 million deaths directly due to diabetes in 2012 (15). Studies have shown that diabetes mellitus is more likely to be due to the lack of vitamin D (16).

On the other hand, approximately half the world's population gets insufficient vitamin D (17). The prevalence of vitamin D deficiency varies according to gender, age, diet, and climate, and skin color (18). Decreased vitamin D level is one of the main factors in predicting the progression of type 2 diabetes (4).

Genetic and environmental factors are associated with the onset of type 2 diabetes (7, 19). Changes in the lifestyle, including unhealthy diet, low physical activity, smoking, consumption of high-fat foods, and reduced consumption of fruits and vegetables have increased the prevalence of type 2 diabetes (20).

In addition to the genetics, hormones and molecular and biochemical factors are effective to develop diabetes (21). The increased levels of triglyceride and cholesterol and decreased levels of high-density lipoprotein (HDL) in diabetics increase the risk of atherosclerosis (22). Type 2 diabetes is more commonly seen in adults, which can be attributed to the increased insulin resistance, being overweight, and low physical activity (20). The higher prevalence of type 2 diabetes in most societies is due to the changes in traditional lifestyle (3).

2. Objectives

This study aimed at reviewing the studies on the relationship between type 2 diabetes and vitamin D deficiency suggesting vitamin D as a preventive factor for type 2 diabetes through glucose homeostasis and insulin sensitivity and resistance.

3. Evidence Acquisition

This review analyzed descriptive, cross-sectional, interventional, and analytical studies through searching the PubMed, Biomed Central, SID, and Iran Doc databases. Specific keywords were used to search the databases in 2 steps through MeSH terms. In the first step, the "type 2 diabetes AND insulin AND vitamin D" and in the next step, more specific keywords, including "insulin resistance AND insulin sensitivity AND pregnancy AND fasting blood sugar" were searched. The searched articles were evaluated according to their titles, abstracts and their reference lists. A total of 11 full-text articles in English and Persian conducted over the past 30 years (from 1986 to 2018) were selected. Figure 1 shows the flow chart of the included articles.

3.1. Inclusion and Exclusion Criteria

The inclusion criteria were descriptive, cross-sectional, interventional, and analytical studies and reviews in the English and Persian language. Studies were evaluated based on their titles and abstracts. Qualitative studies and

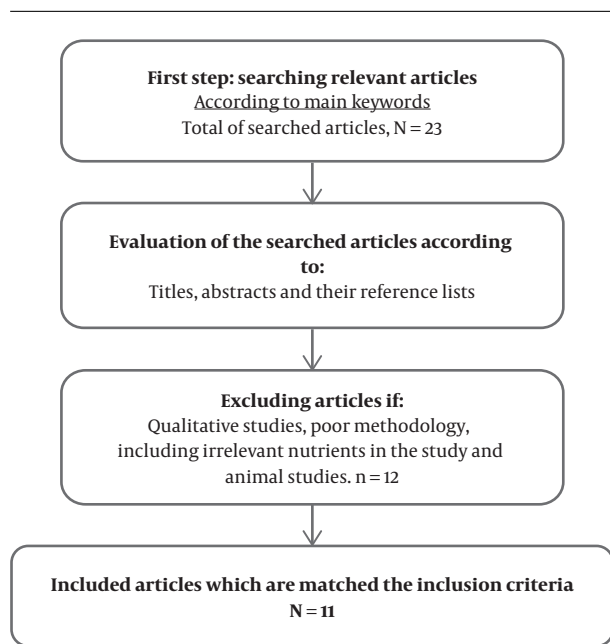


Figure 1. The flow chart of the exclusion and inclusion criteria

irrelevant studies, such as those on type 1 diabetes and the effect of calcium intake on diabetes and also those with improper methodology, specially poor in sample size and also animal studies were excluded. Studies on over 100 participants (up to 400) were included; however, some valuable interventional and/or case-control studies conducted on less than 100 participants were selected. Studies on children (less than 10 years old) and the elderly were not considered.

3.2. Quality Assessment

To evaluate the quality of each study, strengthening the reporting of observational studies in epidemiology (STROBE) statement was used for checking titles, abstracts, introductions, methods, results, and discussions (23) and the studies with a score over 70% were included. Finally, of 23 articles, 12 studies were excluded and 11 articles were analyzed.

4. Results

The results indicated that vitamin D can prevent type 2 diabetes and also it controls glucose homeostasis and insulin sensitivity and resistance. According to the results, the major circulating form of vitamin D is 25-hydroxyvitamin D3, which is an important representative of the vitamin D level in the blood (24). Table 1 represents a summary of the included studies.

A descriptive study on 102 diabetics in the West of Iran stated a significant and positive relationship between the hemoglobin A1c (HbA1C) and fasting blood sugar (FBS) ($P < 0.001$). Approximately, 54% of the patients had suffered from vitamin D deficiency and two-third were female. The findings of the study also showed a significant relationship between the serum level of vitamin D and BMI ($P < 0.05$), however, vitamin D had an inverse relationship with HbA1C, FBS and BMI ($P < 0.05$) (25). A cross-sectional study on patients with 117 type 2 diabetes divided into the groups with 25(OH)D of less than 20 ng/mL, 20 - 30 ng/mL, and more than 30 ng/mL had concluded that vitamin D can control glucose homeostasis and is negatively associated with insulin resistance in type 2 diabetes (16).

Moreover, in a double-blind, placebo-controlled trial on 92 adults treated daily with cholecalciferol (2000 IU) or twice daily with calcium carbonate (400 mg) for 16 weeks had reported an improvement in insulin secretion (62 ± 39 mU; $P = 0.046$). They found that HbA1C in the vitamin D group was increased less than the control group ($P = 0.081$) and concluded that the short-term cholecalciferol supplementation can improve β cell function (27). In addition, in a clinical trial aimed at measuring insulin sensitivity in 100 diabetic patients (30 - 70 years old) from Arak, Iran (13), the patients were given 50,000 units of vitamin D3 for 2 months. They concluded that the serum level of fasting plasma glucose (FPG) increased from 7.6 ± 2.04 to 7.27 ± 2.16 nmol/L in the post-test, whereas the homeostatic model assessment of insulin resistance (HOMA-IR) reduced from 3.57 ± 3.18 to 2.89 ± 3.28 .13. Another randomized controlled trial by Upreti et al. had been conducted on 60 Indian patients with type 2 diabetes with coexisting hypovitaminosis D in 2012 - 2013. The patients had been supplemented with vitamin D for 6 month and results showed a significant decrease in mean HbA1c levels (7.29% to 7.02%; $P = 0.01$) and mean FPG (131.4 to 102.6 mg/dL; $P = 0.04$) (24).

A cross-sectional study had been carried out by Boucher et al. on 44 adults living in East London with an average age of 44.9 years with a glucose intolerance problem and an average vitamin D serum of < 27.5 nmol/L. They determined insulin secretion by the oral glucose tolerance test (OGTT) and concluded that vitamin D had a positive association with insulin and C peptide after an oral glucose challenge (29). In addition, consistent with the current study regarding the association between vitamin D deficiency and diabetes, an interventional study by Gedik et al. had measured insulin secretion in 4 Turkish cases (average age of 32.7 years) with vitamin D deficiency and 10 healthy adults. They employed OGTT to determine the metabolic activity of insulin and glucose and the participants were given oral cholecalciferol (2000 IU/d daily) for 6 months. A significant increase in insulinogenic indices and insulin levels was observed (30).

Table 1. The Characteristics of the Included Studies and Reviews

First Author, Year, Country	Type of Study	No. of Samples	The Studied Population's Characteristics	Intervention	Clinical Outcomes
Ghavam, 2018, Iran (25)	Cross-sectional	102	Diabetics	NA	Vitamin D could improve insulin production.
Khosravi, 2018, Iran (23)	Double-blind clinical trial	50	Overweight and obese women	Oral intake of VD3 and placebo	A 6-w intervention decreased BMI with no effect on FBS and insulin.
Upreti, 2018, India (24)	Randomized clinical trial	60	Patients with T2DM	Oral intake of VD3	VD3 could improve glycemic control and metabolic parameters.
Gulseth, 2017 (26)	Randomized control trial	62	Patients with T2DM	Oral intake of VD3	No significant improvement was observed to control insulin.
Wagner, 2016 (13)	Clinical trial	44	Patients with abnormal glucose tolerance	Oral intake of VD3 and placebo	VD3 did not affect type 2 diabetes
Zhang, 2016, China (16)	Cross-sectional	117	Patients with T2DM	NA	VD3 could control glucose homeostasis, and insulin resistance.
Talaei, 2013, Iran (5)	Clinical trial	100	Patients (30 - 70 y) with T2DM	Oral intake of VD3	An improvement in serum insulin.
Mitri, 2011, US (27)	Clinical trial	92	Adult with high risk of diabetes	Oral intake of VD3 and calcium	A 16-week intervention improved beta-cell function.
Forouhi, 2008, UK (28)	Cross-sectional	524	Nondiabetic men and women (40-69 y)	Measuring serum 25(OH)D and IGF-1	An inverse relationship was found between serum 25(OH)D and glycemic control.
Boucher, 1995 (29)	Cross-sectional	44	Adults with glucose intolerance problem	NA	VD3 had a positive association with insulin.
Gedik, 1986 (30)	Clinical trial	14	Four adults with VD3 deficiency and 10 healthy adults	Administration of 2000 IU/d oral cholecalciferol	A 6-month intervention increased the insulinogenic index and insulin levels.

In contrast, in a cross-sectional study on 524 men and women (40 - 69 years old) had reported that the baseline mean serum 25-hydroxy vitamin D was lower in women (57.2 nmol/L) than men (64.5 nmol/L). The baseline 25-hydroxyvitamin D was inversely associated with the risk of higher fasting glucose and fasting insulin (28). In another double-blind clinical trial, 50 overweight and obese women in the intervention group had received vitamin D supplements (50,000 IU/w) and the other group received a placebo. After 6 weeks of treatment, weight, waist circumference, and BMI were decreased significantly ($P < 0.001$) in the intervention group, however, there was no significant relationship between vitamin D and insulin and also HbA1c and HOMA-IR levels (23). This study also had confirmed that vitamin D deficiency is prevalent in obese cases. In a clinical trial on 44 patients with abnormal glucose tolerance, half of the subjects received 30,000 IU vitamin D3 once a week and a half received a placebo. After the intervention, there was no significant difference between the two groups regarding glycemic control (13). A randomized, double-blind, placebo-controlled trial had been conducted on patients with type 2 diabetes and vitamin D deficiency ($N = 62$) receiving 400,000 IU oral vitamin D3 or placebo for 6 months. For cases in the vitamin D group with the serum 25(OH)D of less than 100 nmol/L, an additional 200,000 IU vitamin D3 had been administered through 4 weeks. Their results showed that there was no

significant relationship between insulin control and vitamin D intake (26).

5. Discussion

This study aimed at finding an association between vitamin D and type 2 diabetes, for example, the effect of vitamin D on insulin secretion, sensitivity, and resistance. Regarding the metabolism of vitamin D, the 25-hydroxylase enzyme in the liver and intestinal microsomes catalyzes the first step of vitamin D activation (31). This process is so crucial, as, by only a small amount of vitamin D in the small intestine or liver, small amounts of pro-vitamin D can be found in the bloodstream (31).

Lack of vitamin D can reduce insulin secretion and its supplementation in animals can maintain secreted insulin (4). Pittas et al. revealed that vitamin D affects glucose homeostasis based on the following observations: (1) the existence of vitamin D dedicated receptors (VDRs) on β cells of pancreas (11); (2) the expression of 1-alpha-hydroxylase enzyme in β cells transforming 25-hydroxyvitamin D to 1.25-hydroxyvitamin D; (3) the existence of VDR on muscle cells; (4) a direct effect of 1.25-hydroxyvitamin D on transcription of insulin receptor gene; and (5) an increase in glucose transferring by insulin *in vitro*.

Vitamin D has shown to cause a 55% relative reduction in the risk of developing type 2 diabetes (4, 27). There was an inverse relationship between vitamin D deficiency and the prevalence of type 2 diabetes in the National Health and Nutrition Examination Survey (NHANES III) during 1988 - 1994 (4). According to the NHANES, regarding race, there was a reverse relationship between the levels of vitamin D and the number of diabetic patients in whites; however, no relationship was found in black subjects (14). In contrast, studies have shown no significant relationship between oral the intake of vitamin D and the level of insulin resistance, which can be bias and they included patients with a deficiency of glucose tolerance without considering the used drugs (13, 26).

Administration of 25-hydroxyvitamin D increases insulin sensitivity up to 54% and its deficiency leads to increased insulin resistance (23). It has indicated that through an optimum intervention period, the oral intake of vitamin D can control insulin (16, 24, 25). These studies tried to conduct a randomized control trial using a large enough sample size. On the other hand, a study measured the weight and BMI means and assessed the role of vitamin D supplementation in reducing obesity. It was found that vitamin D deficiency was more prevalent in obese people with no association with glucose homeostasis. The researchers tried to reduce participants' weight and insulin control was not the only studied variable, as well (23).

Gunal et al. stated that vitamin D3 increased the insulin sensitivity directly in patients with kidney disorder, and subsequently hyperparathyroidism (32). Talaei reported that only a concentration of 100 - 150 nmol/L of vitamin D had a significant effect on insulin sensitivity (5). In contrast, despite the effectiveness of vitamin D, studies have found that the efficacy of vitamin D has been reversed in diabetic patients. For instance, in a study by Taylor and Wise, a high dose of vitamin D increased insulin resistance (33). This study was conducted only on 3 cases with vitamin D deficiency and non-insulin dependent diabetes (33). Although vitamin D injection resulted in a significant increase in vitamin D levels in diabetics, none of them reached the normal levels of vitamin D (17). The differences in results are due to the demographic characteristics of the studied subjects, as well as using experimental methods with different designs to measure insulin secretion and sensitivity (24).

In a study by Orwoll, there was no significant association between vitamin D and insulin secreted following eating in diabetic patients, which can probably be due to the fact that vitamin D cannot be effective for uncontrolled diabetes (11). In interventional studies, different interventions, such as different doses of vitamin D and the selection of specific racial groups, such as Caucasian, can lead to the lack of integrity in findings (11).

Some limitations had been reported in the included studies. Some studies were cross-sectional studies unable to find the accurate effect of vitamin D on insulin secretion. Some studies failed to include optimal sample size and some of them had a time limit. One of the strengths of this review was highlighting the role of vitamin D in glucose homeostasis, as well as insulin resistance. The role of vitamin D is commonly underestimated, whereas it plays a crucial role in type 2 diabetes. It is suggested to consider the role of other determinant factors, such as weight, BMI and calcium intake to develop type 2 diabetes in future studies.

5.1. Conclusions

There was no consensus on the efficacy of vitamin D in the improvement of diabetic patients and the findings were not consistent. In general, based on the results, vitamin D supplementation can reduce insulin resistance in patients with type 2 diabetes and also improve the function of pancreatic β cells. Also, vitamin D deficiency affects insulin response. Vitamin D deficiency is a global health problem, therefore, vitamin D levels in type 2 diabetes should be considered and if needed, vitamin D supplementation should be regarded to control blood sugar and insulin sensitivity.

Supplementary Material

Supplementary material(s) is available [here](#) [To read supplementary materials, please refer to the journal website and open PDF/HTML].

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Footnotes

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