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The Effects of Vitamin D on Obesity, Insulin Resistance and Type 2 Diabetes

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Abstract

Vitamin D is a fat-soluble vitamin. It is also referred to as a steroid hormone with an active form that can bind to receptors. The main way to obtain vitamin D is its synthetization on the skin with the effect of ultraviolet light. It is activated in the body by two hydroxylation reactions in the liver and kidneys. Vitamin D is said to have other effects besides those on the bone metabolism. Vitamin D deficiency is a global social health problem. It is associated with cardiovascular diseases, obesity, metabolic syndrome, type 2 diabetes, various types of cancer, immune deficiencies and increased mortality. It is frequently observed in obese individuals. A possible molecular mechanism of the relationship between obesity and vitamin D deficiency may be associated with the metabolism in mature adipocytes, oxidative stress, inflammation and the gene expression regulation capacity of vitamin D which is related to the adipogenesis process. Vitamin D may lead to an increase in insulin secretion and a decrease in insulin resistance by regulating the immune system. Inflammatory cytokine production is thought to be one of the mechanisms of action of vitamin D on insulin resistance. Inflammatory cytokines appear to be associated with obesity and insulin resistance. Low levels of vitamin D may cause disruption of insulin secretion. Vitamin D may be involved in β-cell secretion activity and changes in tissue response to insulin. There is a relationship between inadequate 25(OH)D levels and β-cell dysfunction. Vitamin D may have beneficial effects on β-cell function by suppressing the renin-angiotensin system. Based on all this information, it may be concluded that vitamin D is associated with obesity, insulin resistance and diabetes, and vitamin D deficiency may form the basis for these conditions.

Keywords: Vitamin D; Obesity; Insulin Resistance

Introduction

Obesity, particularly excess visceral adiposity, is associated with insulin resistance, hyperglycemia, dyslipidemia and hypertension, which together are termed metabolic syndrome. These metabolic disorders increase the risk of development type 2 diabetes mellitus and cardiovascular diseases and contribute to high rates of mortality and morbidity [1,2]. Type 2 diabetes mellitus is the most prevalent metabolic disease in the world, and it is characterized by defects in insulin secretion and a peripheral insulin resistance in the adipose tissue and the liver [3].

Insulin resistance is the condition where the body does not respond appropriately to circulating insulin. It is commonly associated with obesity, hypertension, cardiovascular diseases and type 2 diabetes mellitus. Insulin resistance occurs in several tissues including the liver, muscle and adipose tissue. The liver helps maintaining fasting glucose levels through gluconeogenesis and glycogenolysis. When the liver is insulin-resistant, suppression of hepatic glucose production is impaired, and thus gluconeogenesis and glycogenolysis continue at inappropriately high levels despite normal or high circulating glucose levels. Adipose tissue and muscle are similarly affected by insulin resistance. To compensate for the insulin resistance in these tissues, pancreatic beta-cells produce more insulin. However, there is a limit to how much insulin can be produced, and when this limit has been reached, the beta-cells fail. Type 2 diabetes mellitus occurs when an appropriately low level of insulin is produced in response to a given concentration of glucose [4].

Abdominal obesity is associated with systemic low-grade inflammation [1]. This systemic inflammation may have a role in the pathogenesis of obesity-related metabolic disorders [3]. Systemic inflammatory markers may predict development of type 2 diabetes mellitus in the general population. Adipose tissue appears to play a central role in the induction of inflammation as over-nutrition leads to changes in its cellular composition and production of pro-inflammatory cytokines [1].

The underlying molecular mechanism of the development of insulin resistance is impairment in the insulin signaling pathway in insulin-responsive cells including adipocytes, myocytes, hepatocytes and beta-cells. Normally, when insulin binds to the insulin receptor on these cells, the insulin receptor is auto-phosphorylated at its tyrosine residues, and tyrosine kinase is activated. The insulin receptor then phosphorylates the tyrosine residues on the insulin receptor substrates (IRSs). This leads to linear signaling

cascades that result in protein kinase activation. The activation of protein kinase induces the translocation of GLUT 4 (glucose transporter type 4) and glycogen synthesis, playing an important role in metabolic signaling. Impairment of this insulin signaling cascade may induce insulin resistance and is associated with the development of type 2 diabetes mellitus [4].

Obesity and a low vitamin D status, as well as a positive association between these two parameters, are prevalent world-wide. Additionally, a low vitamin D status was positively correlated with metabolic dysfunction [5].

Vitamin D deficiency is a global social health problem [6-8]. An increase has been observed in the prevalence of vitamin D deficiency due to the decrease in exposure to sun rays because of increased aging, prevalence of sedentary lifestyles and lack of outdoor activities or extensive use of sunblock products in developed societies [7].

Optimal concentration of vitamin D is necessary for growth, development and health. Vitamin D plays an important role in the regulation of calcium levels and the bone metabolism [2].

Recently, vitamin D has been claimed to have other effects besides those on the bone metabolism [7]. Vitamin D deficiency is associated with cardiovascular diseases, obesity, metabolic syndrome, type 2 diabetes, various types of cancer, immune deficiencies and increased mortality [2,7,9]. Vitamin D deficiency may lead to disruptions of insulin secretion and an increase in insulin resistance. Vitamin D supplementation may play a role in the protection of the function of insulin secretion [10]. Vitamin D is believed to be involved in glucose homeostasis, stimulate lipogenesis and modulate cytokine-mediated β-cell apoptosis [11]. Vitamin D has also been reported to influence glucose regulation via its effects on insulin secretion and action. Vitamin D insufficiency, typically assessed by circulating blood levels of 25-hydroxy vitamin D (25(OH)D), has long been suspected as a risk factor for type 1 diabetes [12]. Vitamin D deficiency may cause a greater level of glycaemia and a higher risk of type 2 diabetes mellitus. There is a link between 25(OH)D levels and the insulin responsiveness of tissues as well as between glucose levels and glycosylated hemoglobin (HbA1C) in people without type 2 diabetes mellitus [13]. Obesity has been frequently associated with hypovitaminosis D because of an increased storage of 25(OH) D in adipose tissue, or a reduced sun exposure as the most plausible explanations [14]. Accordingly, a number of previous studies showed an inverse association between 25(OH)D and body mass index (BMI), waist circumference and fat mass as measured by dual-energy X-ray absorptiometry scanning [15-17].

	Severe Deficiency	Deficiency	Inadequacy	Optimal Concentration	Toxicity
Serum 25(OH) D (ng/mL)	0-10	10-20	20-30	30-80	>100

Table 1: Serum Vitamin D Status Classification [7]

In the light of all this information, it may be stated that there is a relationship between vitamin D levels and obesity, insulin resistance and type 2 diabetes mellitus. This study was carried out to reveal the relationship between vitamin D deficiency, obesity, insulin resistance and diabetes among health problems that are increasing today.

Vitamin D Metabolism

Vitamin D is a fat-soluble vitamin [6]. It is also referred to as a steroid hormone with an active form that can bind to receptors [9]. It is considered to be a complex steroid hormonal system regulating calcium balance and involved in autocrine, paracrine and endocrine processes [8]. The parathyroid hormone (PTH), along with 1, 25(OH) 2D which is the active form of vitamin D, is responsible for the regulation of calcium and phosphate balance [6]. It is classically involved in the process of maintaining the calcium and bone balance [10].

There are three ways to maintain adequate storage of vitamin D [6,7]:

1. Sunlight exposure
2. Dietary intake
3. Pharmaceutical supplements

The main source of vitamin D in humans is endogenous biosynthesis in skin cells [10,18]. 80-90% of vitamin D in the body is obtained this way. The dietary supply of vitamin D is much less than the amount obtained through endogenous biosynthesis [7]. Vitamin D in the skin is manifested in the form of 7-dehydrocholesterol (pre-vitamin D). When exposed to ultraviolet sunlight, it is converted to cholecalciferol and vitamin D3 [6,7,9,18]. The dietary and pharmaceutical sources of vitamin D are in the form of vitamin D2 (ergocalciferol) obtained from plant sources and vitamin D3 (cholecalciferol) obtained from animal sources [6,9,10]. Cholecalciferol is mainly found in fish, egg yolk, beef and algae, while ergocalciferol is found in edible mushrooms and alfalfa sprouts. Vitamin D molecules, derived from biologically inactive endogenous and dietary sources, are carried in chylomicrons in blood circulation [10]. Vitamin D undergoes two hydroxylation reactions in the body [9,19]. The vitamin D2 and vitamin D3 that are obtained are mainly exposed to the first hydroxylation in the liver and form 25-hydroxyvitamin D (25[OH] D) [6,7]. The 25-hydroxylase enzyme catalyzes this reaction [10,19]. The formed 25(OH) D has a relatively lower biological activity. It is the primary circulatory form of vitamin D in the body and represents the total vitamin D reserves [6,7,9]. The final activation stage is the second hydroxylation process of 25(OH) D which occurs in the kidneys and produces 1, 25-dihydroxyvitamin D (1, 25[OH] 2D) [6,7]. The enzyme that is responsible for this reaction is 1-hydroxylase [10,19]. 1, 25(OH) 2D is the most biologically active

form of vitamin D, and it is responsible for its physiological functions. 1-α-hydroxylase is the enzyme that is responsible for the reaction of 25(OH) D being converted into 1, 25(OH) 2D in the kidneys [6]. This enzyme is firmly controlled by numerous factors including serum PTH, calcium and phosphate, along with various hormones such as insulin, cortisol, thyroxin, prolactin, growth hormone, androgens and estrogens [6,7,9]. The 1, 25(OH) 2D levels in circulation regulate calcium absorption and bone balance. The serum 25 (OH) D concentrations are 100 times higher than the plasma 1, 25 (OH) 2D concentrations. Additionally, 25(OH) D (2-3 weeks) has a significantly higher half-life than 1, 25(OH) 2D (4-6 hours) [6].

Vitamin D metabolites exert their effects by binding to cytoplasmic vitamin D receptors [6,10,19]. These receptors have a strong affinity for the active form 1, 25(OH) 2D. Vitamin D receptors are expressed by nearly every cell in the body [6,9,19]. The interaction between 1, 25(OH) 2D and receptors stimulates the physiological effects of vitamin D. After binding to the receptors, they are transported to the nucleus, where they interact with specific DNA regions also known as vitamin-D-responsive elements [6].

The serum 25 (OH) D concentrations is the optimal parameter to determine the vitamin D status in the body [6,7,18,19]. It has an inverse correlation to the lipid profile, glucose balance, adiposity and blood pressure [19]. 1,25(OH)2D, which is the active form of vitamin D, is not used to assess the vitamin D status in the body, although it is stronger and has more predisposition towards vitamin D receptors than 25(OH)D [7]. The cut-off point of 25(OH) D is based on the effects of vitamin D on the calcium metabolism. Therefore, low vitamin D levels are associated with decreased intestinal calcium absorption, which in turn causes low serum calcium levels. Consequently, the parathyroid gland is stimulated to secrete PTH, which leads to secondary hyperparathyroidism [6]. The 1,25(OH)2D levels in the body are kept within the referenced range, while they increase as a result of secondary hyperparathyroidism or vitamin D deficiency [7].

Effects of Vitamin D on Health

The relationship between vitamin D deficiency and various chronic illnesses has been proven [6,10,20]. Vitamin D deficiency may play a key role in the pathophysiology of the risk factors for metabolic syndrome, which is a cluster of risk factors embodying insulin resistance, hypertension, atherogenic dyslipidemia and abdominal obesity. It may affect the cardiovascular system, increase insulin resistance and obesity, as well as stimulating the renin-angiotensin-aldosterone system which leads to hypertension [6].

The primary reasons for decreased vitamin D levels in the body are stated below [10,20].

1. Sunlight deprivation (due to factors such as winter season, melatonin, the use of sun protection products or country of residence)
2. The use of various medicines
3. Malabsorption (Crohn's disease, cystic fibrosis, liver disease or celiac disease)
4. Insufficient dietary intake of vitamin D
5. Kidney and liver diseases that may prevent the activation of vitamin D and disrupt its conversion to active metabolites.

Keeping the plasma 25(OH) D levels above 30 ng/mL is considered to be necessary to protect health. To this end, supplement intake and/or more exposure to sunlight are recommended [10]. EFSA (the European Food Safety Authority) considers that a serum 25(OH) D concentration of 50 nmol/L is a suitable target value for all population groups. For adults, an adequate intake for vitamin D is set at 15 μg/day, on this intake level, the majority of the population will achieve a serum 25(OH) D concentration near or above the target of 50 nmol/L. For children aged 1–17 years, an adequate intake for vitamin D is set at 15 μg/day. For infants aged 7–11 months, an adequate intake for vitamin D is set at 10 μg/day. For pregnant and lactating women, EFSA sets the same adequate intake as for non-pregnant non-lactating women, namely 15 μg/day [18].

Effects of Vitamin D on Obesity

Obesity is closely related to inadequate vitamin D levels [2,6,7]. Vitamin D deficiency is prevalent in morbidly obese patients [6,21]. Obese individuals need 2-3 times more vitamin D supplementation for the sufficiency of vitamin D in the body than non-obese individuals [21]. A study showed that the incidence rate of vitamin D deficiency in obese individuals was 49.3% [22]. An inverse correlation between the amount of serum 25(OH) D and adipose cell sizes was reported [8,9]. Increased body fat index and high body mass index (BMI) have a strong inverse correlation with serum 25(OH) D levels [20]. Each unit increase in BMI was associated with a 1.15% decrease in serum 25(OH) D concentrations [21].

A study by Rafiq *et al.* aimed to distinguish the specific contributions of total body fat (TBF), abdominal subcutaneous adipose tissue (aSAT), visceral adipose tissue (VAT) and hepatic fat on 25(OH)D concentrations [23]. TBF was inversely associated with 25(OH) D concentrations in women, but not in men. One percent higher TBF was associated with 0.40 nmol/L (95%CI: 0, 67 to 0, 13) lower 25(OH) D. aSAT was not associated with 25(OH) D concentrations. One cm2 higher VAT was associated with 0.05 nmol/L (0.09 to 0.02) lower 25(OH) D in men, and 0.06 nmol/L (0.10 to 0.01) lower 25(OH) D in women. Hepatic fat was only associated with 25(OH) D in men. A tenfold increase in hepatic fat was associated with 6.21 nmol/L (10.70 to 1.73) lower 25(OH)D. Regressions with standardized values showed VAT was most strongly related to 25(OH)D. Vitamin D may have an effect on the differentiation process of adipose tissue cells, and this way, preadipocytes become mature adipocytes. In human cells, vitamin D stimulates the formation of adipose cells by increasing the gene expressions of lipogenesis enzymes such as fatty

acid synthase (FASN), fatty acid binding protein (FABP) and peroxisome proliferator-activated receptor-γ (PPARγ), which is the primary transcription factor involved in adipogenic differentiation [2].

In general, 25(OH) D and 1, 25(OH) 2D may support adipogenic differentiation for mature adipocytes based on the presence of 1-α-hydroxylase in mature adipose cells. Additionally, 1, 25(OH) 2D may stimulate the translocation of glucose transporter-4 (GLUT4) into the membrane, support adiponectin secretion and production of normal adipocyte genes such as leptin and inhibit the production of uncoupling proteins. Thus, vitamin D receptors directly inhibit the production of UCP1 (uncoupling protein-1), which is a critical protein for fatty acid oxidation in brown adipose tissue [2].

Obesity is strongly associated with low-level inflammation, expression of inflammatory markers and their secretion [2,21]. Vitamin D was demonstrated to be able to decrease inflammation [21]. 1, 25(OH) 2D, its active form, induces anti-inflammatory effects on adipocytes. This vitamin supports lower chemokine and cytokine secretion by adipocytes. It regulates the secretion of adipokines such as adiponectin, leptin, and resistin in adipocytes [2]. Serum levels of adiponectin decrease with obesity and are positively associated with insulin sensitivity [24]. Plasma adiponectin levels may be low in individuals with visceral obesity [25]. Adiponectin has anti-inflammatory effects. It is the primary adipokine secreted by adipocytes. Vitamin D is associated with decreased adiponectin levels [2]. In a study by Haidari *et al.* the mean serum concentration of 25(OH)D was 11.01±5.55 ng/mL [26]. Severe deficiency, deficiency and insufficiency of vitamin D were detected in 60.71%, 35.72%, and 3.57% of the participants, respectively. The results showed that those in the lowest group of serum 25(OH)D levels had significantly higher TNF-α values (5.05±9.62 pg/mL) than those in the group with the highest serum 25(OH)D levels (0.31±0.54 pg/mL) (P=0.026).

Vitamin D causes decreasing effects on cytokine secretion stimulated by visceral adipose tissue instead of subcutaneous adipose tissue. In obese individuals, there are low levels of adenosine monophosphate-activated protein kinase (AMPK) in visceral adipose tissue. AMPK may increase sirtuin 1 by raising the NAD/NADH (nicotinamide adenine dinucleotide/reduced nicotinamide adenine dinucleotide) ratio and decrease adipose tissue macrophage infiltration and inflammation. Vitamin D deficiency significantly decreases the mRNA levels of oxidation-dependent genes. In obese rats fed with an insufficient vitamin D diet, sirtuin 1 and AMPK activities were demonstrated to decrease. Vitamin D plays a beneficial role in the adipocyte metabolism and obesity progression [2].

Vitamin D causes a decrease in proinflammatory cytokine levels. There is a negative association between plasma interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) levels. The active form 1, 25(OH) 2D may decrease the levels of inflammatory markers such as monocyte chemotactic protein-1 and interleukin 1 β (IL-1 β). Therefore, it may decrease TNF-α-stimulated proinflammatory marker expression [2]. In a study, the effect of vitamin D supplementation on CRP was investigated in individuals with vitamin D levels below 50 nmol/L. Baseline, one month after and 3 month after supplementation CRP levels were 1.6 ± 2.0 mg/L, 2.6 ± 6.7 mg/L (P=0,16)*, 1,3 ± 2.1 mg/L (P=0.11)*, respectively [27].

To sum up, vitamin D plays an important role in inflammatory conditions in adipocytes and adipose tissue. This effect is due to its capability to decrease the phosphorylation and translocation of nuclear factor-kappa B (NF-κB) into the nucleus, and consequently, decrease proinflammatory and oxidative stress markers [2].

A possible molecular mechanism of the relationship between obesity and vitamin D deficiency may be constituted by the metabolism in mature adipocytes, oxidative stress, inflammation and gene expression regulation capacity of vitamin D, which is related to the adipogenesis process [2].

Possible reasons for decreased vitamin D levels in obesity are as follows [6]:

1. Insufficient vitamin D intake
2. Inadequate exposure to sunlight
3. Decreased intestinal vitamin D absorption, especially in individuals having undergone bariatric surgery.

The active form 1, 25(OH) 2D assumes a role in the modulation of inflammation, adipose cell formation and metabolic syndrome. Obesity may lead to decreased vitamin D levels. However, a predisposition towards vitamin D deficiency does not cause obesity, and increased vitamin D levels cannot reverse obesity [7]. Adipose tissue is the primary storage place for vitamin D. This tissue performs vitamin D secretion and produces vitamin D receptors and enzymes involved in the vitamin D metabolism [2]. Some scientists think vitamin D is kept within adipose tissue since it is a fat-soluble vitamin, in which case, the amount of circulated vitamin D is lower. Obese individuals are in more need of vitamin D than other individuals [7]. Adipose tissue cells react when they are exposed to 1,25(OH)2D, and the reserves of vitamin D in adipose tissue are proportionate to its plasma concentration and release it at a much lower rate that is proportionate to its concentration in adipose tissue [2].

Vitamin D supplementation may lead to decreased body fat mass and increased serum vitamin D concentration [2,6]. It may provide protection against diet-induced obesity by increasing fatty acid oxidation [8].

Effects of Vitamin D on Insulin Resistance and Insulin Sensitivity

Insulin resistance is defined as a decreased biological response to insulin [8]. Vitamin D deficiency is associated with insulin

resistance or disrupted insulin secretion [6,8]. Vitamin D provides assistance in decreasing insulin resistance and proinflammatory cytokine amounts, improving β-cell function and increasing insulin secretion and sensitivity [7,28,29]. Increased circulating 25(OH) D concentration is associated with decreased prevalence of insulin resistance [30]. Vitamin D deficiency is related to insulin resistance [31]. Vitamin D appears to increase insulin sensitivity through various mechanisms. Vitamin D deficiency activates the increase of NF-κB, TNF-α, cytokine secretion and inflammation, and it may lead to an increase in parathyroid hormone levels [32]. Vitamin D has anti-inflammatory and immune system regulation effects. It may provide an increase in insulin secretion and decrease in insulin resistance by regulating the immune system. Inflammatory cytokine expression is thought to be one of the mechanisms of action of vitamin D on insulin resistance. Inflammatory cytokines are associated with obesity and insulin resistance [31]. Vitamin D and 1, 25(OH) 2D act as anti-inflammatory agents. For example, 1, 25(OH) 2D inhibits the release of the pro-inflammatory cytokine TNF-α and regulates the activity of NF- κB, which functions as a mediator of TNF-α pro-inflammatory activity on multiple levels. Additionally, 1, 25(OH) 2D down-regulates the increased levels of inflammatory markers (TNF-α, IL-6, IL-1, IL-8, cyclo-oxygenase-2, intercellular adhesion molecule-1 and B7-1) in monocytes from type 2 diabetic patients in comparison to monocytes from healthy controls. In other models, 1, 25(OH) 2D inhibits the synthesis and activities of pro-inflammatory prostaglandin (PG) by inhibiting cyclooxygenase-2 expression, increasing the expression of the enzyme which inactivated PG (15-PG dehydrogenase) and decreasing PG receptors. 1, 25(OH) 2D affects several pathways known to regulate inflammatory responses, including increasing mitogen-activated protein kinase phosphatase 5 which down-regulates p38 mitogen-activated protein kinase activity. Therefore, vitamin D may also function to reduce the risk of diabetes by reducing inflammatory responses [33].

Vitamin D receptor cells and 1-α-hydroxylase are found in the pancreas, where the mechanisms that enable 25(OH) D to be converted into 1, 25(OH) 2D are formed [6]. The active form 1, 25(OH) 2D appears to directly increase insulin sensitivity by stimulating the expression of insulin receptors [29,34]. The active vitamin D directly activates insulin receptor gene transcription, stimulates the expression of insulin receptors and increases glucose transportation mediated by insulin [34]. It can also increase insulin sensitivity by activating PPARγ. This factor is a transcription factor that is involved in the regulation of the fatty acid metabolism in insulin-sensitive tissues. Vitamin D can indirectly affect insulin sensitivity through the regulation of the calcium balance. Calcium is known to change intracellular processes in insulin-sensitive tissues. Intracellular calcium concentration and calcium flux mediated by vitamin D may disrupt insulin signal transduction, which is responsible for glucose transportation activity. Vitamin D deficiency leads to increased parathyroid hormone concentration, which is associated with insulin resistance. Vitamin D leads to the improvement of insulin sensitivity through the renin-angiotensin-aldosterone system. Angiotensin II is considered to contribute to insulin resistance through various mechanisms in skeletal muscles including the activation of NF-κB. Vitamin D deficiency was associated with increased fat infiltration in skeletal muscles independently of body mass, and this leads to decreased insulin action [29].

Vitamin D also assumes a role in insulin signalization. Serum 25(OH) D levels have an inverse correlation with the intensity of insulin resistance and blood sugar concentration. The existence of vitamin D receptors in pancreatic β-cells supports the theory that vitamin D affects insulin synthesis and secretion [20].

Adipose tissue generally acts as an endocrine organ involved in the glucocorticoid hormone metabolism. Dysregulation of this mechanism may lead to obesity, dyslipidemia, hypertension and diabetes. In general, in the presence of triacylglycerols, which cause decreased glucose uptake by insulin-sensitive tissues, insulin sensitivity is reduced. Regulating vitamin D levels in the body has positive effects on increased insulin sensitivity and insulin receptor phosphorylation [34].

A negative association was determined between serum 25(OH) D and insulin resistance index values. There is also a negative association between serum 25(OH) D concentration and fasting insulin levels [6]. Optimal 25(OH) D balance is necessary for insulin activity and secretion. A study determined a negative association between HOMA, insulin sensitivity and serum 25(OH) D levels independent of age, BMI and waist circumference [35]. In a study carried out by Li *et al.* [36], serum 25(OH) D concentration was determined to have an inverse correlation with fasting insulin, HbA1c, and HOMA-IR levels. In another study, 81 healthy individuals aged 20-69 were divided into 2 groups. One of these groups received 420 IU/day vitamin D, and the other group received placebo for 12 months. At the beginning of the study, the HOMA-IR values of the individuals in the vitamin d and the placebo group were calculated as 1.17±1.08 and 1.29±1.08 respectively. At the end of 12 months, the HOMA-IR values were found to be 0.84±1.09 and 1.12±1.09 respectively. The change in the HOMA-IR values of the vitamin D supplementation group was statistically significant ($p < 0.05$) [30]. A study on rats that were fed a high-fat diet by Park *et al.* [37] investigated the effects of 3 different vitamin D doses on HOMA-IR. The rats were divided into 3 groups and fed with a high-fat diet containing 25 UI/kg, 100 UI/kg and 10000 UI/kg cholecalciferol for 8 weeks. At the end of the study, the serum insulin, HOMA-IR and insulin sensitivity mean values of 25 IU/kg, 100 IU/kg and 10000 IU/kg vitamin D groups were found as 4.8±0.6 ng/mL, 3.9±0.4 ng/mL 4.4±0.5 ng/mL; 10.8±1.2, 8.4±0.9, 9.2±1.0, 5.7±0.7 μmol glucose/min/100 g/per μmol insulin/l, 8.7±1.0 μmol glucose/min/100 g/per μmol insulin/l, 7.3±0.9 μmol glucose/min/100 g/per μmol insulin/l, respectively. The HOMA-IR value was found to be the highest, and insulin sensitivity was the lowest in rats with low-dose vitamin D supplementation ($p < 0.05$).

Vitamin D supplementation has beneficial effects on improvement of insulin resistance [6,21]. In the post-supplementation period, decreased insulin resistance and increased insulin sensitivity are observed [38]. Supplementation may improve glycemic control

by decreasing the insulin resistance index (HOMA-IR) levels [21,32]. In a study, vitamin D supplementation was demonstrated to improve serum glucose, triglyceride, insulin, and HOMA-IR indices [39].

Effects of Vitamin D on Type 2 Diabetes

Vitamin D deficiency was linked to the onset of diabetes [40]. Vitamin D deficiency is seen to be in higher levels in type 1 and type 2 diabetes patients in comparison to healthy individuals [7]. It was shown to be associated with decreased insulin secretion and type 2 diabetes [28]. In a study by Pan *et al.,* the serum 25 (OH) D values of 270 adult type 2 diabetic individuals were examined. The mean level of serum 25(OH)D was 22.93 ng/mL, and the percentages of vitamin D deficiency and insufficiency were 43.71% and 36.63%, respectively [41]. Serum 25(OH) D levels are related to the incidence rates of type 2 diabetes [21]. Low levels of serum vitamin D are associated with disrupted glucose balance [7]. Low levels of vitamin D may lead to disruptions in insulin secretion and increase peripheral insulin resistance, which are regarded as two main risk factors for the development of type 2 diabetes [10].

Vitamin D may reduce the formation of diabetes in two ways [10]:

1. Providing changes in the hepatic glucose and lipid metabolism
2. Supporting the pancreas islet function and its survival

Diabetes is initiated by the onset of insulin resistance. β-cells can overcome this resistance by releasing more insulin, thus preventing hyperglycemia. However, as this hyperactivity increases, the β-cells experience excessive Ca2+ and reactive oxygen species (ROS) signaling that results in cell death and onset of diabetes. Vitamin D deficiency contributes to both the initial insulin resistance and the subsequent onset of diabetes caused by β-cell death. Vitamin D acts to reduce inflammation, which is a major process in inducing insulin resistance. Vitamin D maintains the normal resting levels of both Ca2+ and ROS that are elevated in the β-cells in diabetes [40]. Pancreas islet cells include both vitamin D receptors and vitamin D-dependent calcium-binding proteins. Insulin secretion is associated with changes in intracellular calcium concentration [9]. Calcium is necessary for insulin secretion [7]. Changes in intracellular calcium concentration may affect intracellular insulin responses [9]. Supplementation of the active form 1, 25(OH) 2D leads to increased insulin secretion, which may also be caused by an increase in the intracellular calcium levels. B-cells carry calcium-binding proteins, the presence of which supports the mediation of calcium. Active vitamin D metabolites may lead to a change in beta-cell growth and differentiation. Vitamin D deficiency may cause secondary hyperparathyroidism. High PTH concentrations may cause glucose intolerance [28].

Vitamin D also has a very significant role in maintaining the epigenome. Epigenetic alterations are characteristics of diabetes by which many diabetes-related genes are inactivated by hyper methylation. Vitamin D functions in preventing such hyper methylation by increasing the expression of the DNA demethylases that prevent hyper methylation of multiple gene promoter regions of many diabetes-related genes. What is remarkable is just how many cellular processes are maintained by Vitamin D. When Vitamin D is deficient, many of these processes begin to decline, and this sets the stage for the onset of diseases such as diabetes [40].

Vitamin D is involved in the process of maintaining insulin secretion, and it may also be involved in β-cell secretion activities and changes in tissue responses to insulin [7,9]. Inadequate 25(OH) D levels are associated with β-cell dysfunction [8]. Vitamin D may have beneficial effects on β-cell function by suppressing the renin-angiotensin system [10]. Insulin-expressing β-cells produce genes involved in vitamin D metabolism, vitamin D-binding proteins, and vitamin D receptors which are related to glucose tolerance, insulin receptors, insulin secretion, insulin sensitivity, and inflammation [7]. In a study by Niroomand *et al.,* 162 individuals with vitamin D deficiency were divided into 2 groups [42]. One group received 50000 UI/day vitamin D, and the control group received placebo for six months. Fasting plasma glucose level and 2-hour oral glucose tolerance test plasma glucose level at baseline and at the end of the supplementation process were 107 ± 6 mg/dL, 100 ± 8 mg/dL, 141 ± 27 mg/dL, 129 ± 2 mg/dL, respectively. After vitamin D supplementation, fasting plasma glucose level and 2-hour oral glucose tolerance test decreased in plasma glucose level, but the difference was not statistically significant.

Systemic inflammation plays a significant role in the pathogenesis of type 2 diabetes through proinflammatory cytokines. Vitamin D may degrade the effects of inflammation on the risk of diabetes in various ways. The active form 1, 25(OH) 2D can improve insulin sensitivity and has protective effects against β-cell apoptosis increased by cytokines by directly changing the activity and production processes of cytokines. A course that it follows to this end involves decreasing NF-κB, which is the primary transcription factor for TNF-α and other inflammatory mediators. Another potential route of the antiapoptotic effects of the active form 1,25(OH)2D on β-cells is considered to be through counteracting cytokine-induced expression [29].

Changes in genes involved in the vitamin D metabolism and synthesis of vitamin D receptors were associated with disrupted glucose intolerance, decreased insulin secretion, reduced insulin sensitivity and increased inflammation [8].

The correlation between vitamin D and diabetes may be summarized as follows [20]:

1. B-cells in the pancreas contain vitamin D receptors.
2. 1,25(OH)2D stimulates insulin secretion.

3. Insulin secretion in individuals with vitamin D deficiency is reduced.
4. Vitamin D is associated with the physiological functions of pancreatic β-cells.
5. Vitamin D receptors and 1-α-hydroxylase are produced in the pancreatic islet tissue.
6. Vitamin D deficiency can disrupt insulin expression mediated by glucose.
7. Insulin secretion is dependent on calcium whose balance, in turn, is dependent on vitamin D.
8. Vitamin D deficiency increases in parallel with diabetes.

Vitamin D supplementation has positive effects on oral glucose tolerance [2,21]. It can improve glycemic control by decreasing fasting plasma glucose and glycated hemoglobin (HbA1c) levels. Daily doses of 4000 IU can bring serum 25(OH) D levels to >40 mg/mL. This dosage is recommended for type 2 diabetes patients for improving their glycemic index values [21].

Conclusion

Vitamin D is a fat-soluble vitamin. It is also referred to as a steroid hormone with an active form that can bind to receptors. Vitamin D can exert other types of effects besides those on the bone metabolism. Vitamin D deficiency is a global social health problem. It is associated with cardiovascular diseases, obesity, metabolic syndrome, type 2 diabetes, various types of cancer, immune deficiencies and increased mortality. Due to its inflammatory effects and involvement in the processes of insulin synthesis and secretion, vitamin D is associated with obesity, insulin resistance and diabetes. Individuals at risk of vitamin D deficiency, obesity, insulin resistance or diabetes, and patients suffering from the aforementioned disorders are recommended to expose themselves to more sunlight, take high amounts of dietary vitamin D, and if the deficiency is too severe, use vitamin D supplements.

References

1. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N (2014) Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clinic Pract 105: 141-50.

2. Ruiz-Ojeda FJ, Anguita-Ruiz A, Leis R, Aguilera CM (2018) Genetic Factors and Molecular Mechanisms of Vitamin D and Obesity Relationship. Ann Nutr Metab 73: 89-99.

3. Shoelson SE, Lee J, Goldfine AB (2006) Inflammation and insulin resistance. J Clin Invest 116: 1793-801.

4. Lee BC, Lee J (2014) Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. Biochim Biophys Acta 1842: 446-62.

5. Cordeiro A, Santos A, Bernardes M, Ramalho A, Martins MJ (2017) Vitamin D metabolism in human adipose tissue: could it explain low vitamin D status in obesity? Horm Mol Biol Clin Investig 33: 446-62.

6. Prasad P, Kochhar A (2016) Interplay of vitamin D and metabolic syndrome: A review. Diabetes Metab Syndr 10: 105-12.

7. Matyjaszek-Matuszek B, Lenart-Lipinska M, Wozniakowska E (2015) Clinical implications of vitamin D deficiency. Prz Menopauzalny 14: 75-81.

8. Lima-Martinez MM, Arrau C, Jerez S, Paoli M, Gonzalez-Rivas JP, et al. (2017) Relationship between the Finnish Diabetes Risk Score (FINDRISC), vitamin D levels, and insulin resistance in obese subjects. Prim Care Diabetes 11: 94-100.

9. Wallace IR, Wallace HJ, McKinley MC, Bell PM, Hunter SJ (2016) Vitamin D and insulin resistance. Clin Endocrinol (Oxf) 84: 159-71.

10. Leung PS (2016) The Potential Protective Action of Vitamin D in Hepatic Insulin Resistance and Pancreatic Islet Dysfunction in Type 2 Diabetes Mellitus. Nutrients 8: 147.

11. Dutta D, Mondal SA, Choudhuri S, Maisnam I, Hasanoor Reza AH, et al. (2014) Vitamin-D supplementation in prediabetes reduced progression to type 2 diabetes and was associated with decreased insulin resistance and systemic inflammation: An open label randomized prospective study from Eastern India. Diabetes Res Clin Pract103: e18-e23.

12. Khan H, Kunutsor S, Franco OH, Chowdhury R (2013) Vitamin D, type 2 diabetes and other metabolic outcomes: a systematic review and meta-analysis of prospective studies. Proc Nutr Soc 72: 89-97.

13. Grineva EN, Karonova T, Micheeva E, Belyaeva O, Nikitina IL (2013) Vitamin D deficiency is a risk factor for obesity and diabetes type 2 in women at late reproductive age. Aging (Albany NY) 5: 575-81.

14. Bellia A, Garcovich C, D'Adamo M, Lombardo M, Tesauro M, et al. (2013) Serum 25-hydroxyvitamin D levels are inversely associated with systemic inflammation in severe obese subjects. Intern Emerg Med 8: 33-40.

15. Vilarrasa N, Maravall J, Estepa A, Sanchez R, Masdevall C, et al. (2007) Low 25-hydroxyvitamin D concentrations in obese women: their clinical significance and relationship with anthropometric and body composition variables. J Endocrinol Invest 30: 653-8.

16. McGill AT, Stewart JM, Lithander FE, Strik CM, Poppitt SD (2008) Relationships of low serum vitamin D3 with anthropometry and markers of the metabolic syndrome and diabetes in overweight and obesity. Nutr J 7:4.

17. Arunabh S, Pollack S, Yeh J, Aloia JF (2003) Body fat content and 25-hydroxyvitamin D levels in healthy women. J Clin Endocrinol Metab 88: 157-61.

18. Bresson JL, Burlingame B, Dean T, Fairweather-Tait, S, Heinonen M, et al. (2016) Dietary reference values for vitamin D. EFSA J 14: e04547.

19. Ju SY, Jeong HS, Kim DH (2014) Blood vitamin D status and metabolic syndrome in the general adult population: a dose-response meta-analysis. J Clin Endocrinol Metab 99: 1053-63.

20. Wimalawansa SJ (2018) Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. J Steroid Biochem Mol Biol 175: 7-89.

21. Mirhosseini N, Vatanparast H, Mazidi M, Kimball SM (2017) The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients: A Meta-Analysis. J Clin Endocrinol Metab 102: 3097-110.

22. Gouda W, Mageed L, Shaker Y, Hamimy WI, Afify M (2018) Assessment of Serum Vitamin D and Irisin Levels in Obese Patients. Clin Lab 64.

23. Rafiq R, Walschot F, Lips P, Lamb HJ, de Roos A, et al. (2018) Associations of different body fat deposits with serum 25-hydroxyvitamin D concentrations. Clin Nutr 10.

24. Achari AE, Jain SK (2017) Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction. Int J Mol Sci 18: E1321.

25. Moon HU, Ha KH, Han SJ, Kim HJ, Kim DJ (2019) The Association of Adiponectin and Visceral Fat with Insulin Resistance and beta-Cell Dysfunction. J Korean Med Sci 34: e7.

26. Haidari FP, Zakerkish MD, Karandish MP, Saki AP, Pooraziz SM (2016) Association between Serum Vitamin D Level and Glycemic and Inflammatory Markers in Non-obese Patients with Type 2 Diabetes. Iran J Med Sci 41: 367-73.

27. Ojaimi S, Skinner NA, Strauss BJ, Sundararajan V, Woolley I, et al. (2013) Vitamin D deficiency impacts on expression of toll-like receptor-2 and cytokine profile: a pilot study. J Transl Med 11: 176.

28. Lips P, Eekhoff M, van Schoor N, Oosterwerff M, de Jongh R, et al. (2017) Vitamin D and type 2 diabetes. J Steroid Biochem Mol Biol 173: 280-5.

29. Angellotti E, Pittas AG (2017) The Role of Vitamin D in the Prevention of Type 2 Diabetes: To D or Not to D? Endocrinol 158: 2013-21.

30. Sun X, Cao ZB, Tanisawa K, Ito T, Oshima S, et al. (2016) Vitamin D supplementation reduces insulin resistance in Japanese adults: a secondary analysis of a double-blind, randomized, placebo-controlled trial. Nutr Res 36: 1121-9.

31. Kelishadi R, Salek S, Salek M, Hashemipour M, Movahedian M (2014) Effects of vitamin D supplementation on insulin resistance and cardiometabolic risk factors in children with metabolic syndrome: a triple-masked controlled trial. J Pediatr (Rio J) 90: 28-34.

32. Banerjee A, Khemka VK, Roy D, Poddar J, Roy TKS, et al. (2017) Role of Serum Adiponectin and Vitamin D in Prediabetes and Diabetes Mellitus. Can J Diabetes 41: 259-65.

33. Teegarden D, Donkin SS (2009) Vitamin D: emerging new roles in insulin sensitivity. Nutr Res Rev 22: 82-92.

34. Elseweidy MM, Amin RS, Atteia HH, Ali MA (2017) Vitamin D3 intake as regulator of insulin degrading enzyme and insulin receptor phosphorylation in diabetic rats. Biomed Pharmacother 85: 155-9.

35. Tanczer T, Magenheim R, Furst A, Domjan B, Janicsek Z, et al. (2017) The Relationship between 25-hydroxyvitamin D Levels, Insulin Sensitivity and Insulin Secretion in Women 3 Years after Delivery. Can J Diabetes 41: 621-7.

36. Li D, Wei H, Xue H, Zhang J, Chen M, et al.(2018) Higher serum 25(OH)D level is associated with decreased risk of impairment of glucose homeostasis: data from Southwest China. BMC Endocr Disord 18: 25.

37. Park S, Kim DS, Kang S (2016) Vitamin D deficiency impairs glucose-stimulated insulin secretion and increases insulin resistance by reducing PPAR-gamma expression in nonobese Type 2 diabetic rats. J Nutr Biochem 27: 257-65.

38. Gupta T, Rawat M, Gupta N, Arora S (2017) Study of Effect of Vitamin D Supplementation on the Clinical, Hormonal and Metabolic Profile of the PCOS Women. J Obstet Gynaecol India 67: 349-55.

39. Mazzone G, Morisco C, Lembo V, D'Argenio G, D'Armiento M, et al. (2018) Dietary supplementation of vitamin D prevents the development of western diet-induced metabolic, hepatic and cardiovascular abnormalities in rats. United European Gastroenterol J 6: 1056-64.

40. Berridge MJ (2017) Vitamin D deficiency and diabetes. Biochem J 474: 1321-32.

41. Pan GT, Guo JF, Mei SL, Zhang MX, Hu ZY, et al. (2016) Vitamin D Deficiency in Relation to the Risk of Metabolic Syndrome in Middle-Aged and Elderly Patients with Type 2 Diabetes Mellitus. J Nutr Sci Vitaminol (Tokyo) 62: 213-9.

42. Niroomand M, Fotouhi A, Irannejad N, Hosseinpanah F (2019) Does high-dose vitamin D supplementation impact insulin resistance and risk of development of diabetes in patients with pre-diabetes? A double-blind randomized clinical trial. Diabetes Res Clini Prac 148: 1-9.