

Review: How Vitamin D Supplementation Improve Insulin Sensitivity in Patients with Metabolic Syndrome

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ABSTRACT

The metabolic syndrome is a group of cardio metabolic risk factors characterized by adipose tissue malfunction and insulin resistance. Insulin resistance might be one of the main reasons of many metabolic disturbances as well as dysregulation of the blood glucose level. In recent years, the relationship between vitamin D and insulin resistance has been a topic of debate and growing broad interest. In fact, vitamin D serum level may be one of the factors accelerating the development of insulin resistance. Vitamin D deficiency is a common abnormal condition in the population and may be involved with the pathogenesis of diseases related to insulin resistance, such as obesity, diabetes, hyperlipidemia and polycystic ovary syndrome (PCOS). In addition, there are several researches that recommended the use of vitamin D to improve insulin resistance in patients with metabolic disorders, but the mechanism by which the vitamin works to produce this effect is still a matter of debate among researchers. the aim of this review is to summarize the recent evidence suggest mechanisms by which vitamin D can improves insulin sensitivity.

Keywords- 25-hydroxyvitamin D; vitamin D receptor; insulin resistance; homeostasis model assessment of insulin resistance (HOMA-IR); type 2 diabetes; obesity; metabolic syndrome; polycystic ovary syndrome.

I. INTRODUCTION

Vitamin D has extremely important functions in the body as it acts as a hormone like substance so it affects different systems in human body. It acts as a chemical messenger and is involved in the regulation of transcription and transcriptional modifications in more than 3% of the human genome ⁽¹⁾. Almost all body tissues and organs have receptors for vitamin D, and it appears to be involved in many biological functions. The permeant existence of CYP27B1, along with the vitamin D receptor in several tissues, suggests that vitamin D could have another important function beyond bone metabolism ^(2,3).

On the other hand, vitamin D supplementation may also improve the lipid profile as reported by Jamilian et al., who found a reduction of TG and very low-density lipoprotein cholesterol (LDL-C) associated

with vitamin D supplementation ⁽⁴⁾. Imga et al. also found an improvement in HOMA-IR and LDL-C in both obese and overweight women supplemented with vitamin D3 ⁽⁵⁾.

Vitamin D deficiency is one of the key public health issues globally. It is estimated that about 1 billion people worldwide have low blood levels of vitamin D ⁽⁶⁾. In several cross-sectional studies, a low blood level of vitamin D was found to be associated with a higher incidence of insulin resistance, diabetes mellitus, obesity and polycystic ovary. Intervention studies have not adequately identified or observed correlations between vitamin D deficiency and poor glucose tolerance and diabetes in humans. If vitamin D treatment improves glucose metabolism, these benefits are most likely to be seen in patients who have low levels of the vitamin, and the results therefore are inconclusive ⁽⁷⁻⁹⁾.

II. VITAMIN D AND INSULIN RESISTANCE

Vitamin D levels have been linked to a variety of disturbances including insulin resistance, hormonal modulation involves insulin metabolism and reproductive control. Vitamin D is hypothesized to influence the development of metabolic abnormalities through gene transcription. Reduced 25(OH)D levels have been linked to insulin resistance, menstrual abnormalities, hyperandrogenism, obesity, and increased cardiovascular disease risk factors in observational studies⁽¹⁰⁾. Vitamin D has effects that are mediated by both genetic and cellular processes. Vitamin D controls gene transcription via nuclear VDRs found throughout the body, including the bones, parathyroid glands, and ovaries⁽¹¹⁾. The effects of VDRs on LH and SHBG levels have been connected to the pathophysiology of PCOS. Testosterone levels, insulin resistance and insulin levels in the blood^(12,13). It's been proposed that a combination of vitamin D deficiency and dietary calcium inadequacy may be to blame for the PCOS-related menstrual irregularities⁽¹⁴⁾.

One possibility is that vitamin D helps to improve the function of beta cells in the pancreas, which are responsible for producing insulin. Studies have shown that vitamin D can increase insulin secretion from beta cells, which may help to improve glucose tolerance and insulin sensitivity⁽¹⁵⁾.

The exact mechanism by which vitamin D improves insulin resistance is not completely clear, but there are several suggested mechanisms that could be involved include:

III. VITAMIN D ROLES IN REGULATION OF CALCIUM HOMEOSTASIS

Vitamin D is involved in the regulation of calcium homeostasis, which may impact insulin sensitivity. Calcium influx has been suggested to be involved in insulin action, and studies have shown that a low calcium concentration in cells can lead to insulin resistance. Vitamin D helps maintain optimal calcium concentrations in cells, which may improve insulin sensitivity⁽¹⁶⁾. The stimulatory effects of vitamin D on insulin secretion may only manifest when calcium levels are adequate. Insulin secretion is a calcium-dependent process, and therefore alterations in calcium flux can have adverse effects on β -cell secretory function. Glucose-stimulated insulin secretion has also been found to be lower in vitamin D-deficient rats when concurrent hypocalcemia has not been corrected⁽¹⁷⁾. Two vitamin D-mediated signaling pathways are involved in this process. The first includes PKA activation that phosphorylates various proteins engaged in the function of L-type voltage-dependent Ca^{2+} channels associated

with insulin secretion. The second engages PLC synthesis and the activation of inositol triphosphate (InsP3) triggering the secretion of Ca^{2+} from ER leading to DAG synthesis. Subsequently, DAG activates PKC that is responsible for the phosphorylation of the KATP channels and L-type voltage-dependent Ca^{2+} channels. The latter trigger the depolarization of cytoplasmic membrane and opening of T-type Ca^{2+} and L-type channels that in consequence leads to the elevation of intracellular Ca^{2+} followed by insulin secretion⁽¹⁸⁾.

IV. ANTI-INFLAMMATORY EFFECTS OF VITAMIN D

Chronic inflammation is involved in the development of insulin resistance, which increases the risk of type 2 DM. VDR is known to be expressed by macrophages and dendritic cells, suggesting that vitamin D plays an important role in the modulation of inflammatory responses⁽¹⁹⁾. Vitamin D has anti-inflammatory effects, and inflammation is known to be a factor in the development of insulin resistance. Vitamin D may help reduce the levels of inflammatory markers in the body, thereby improving insulin sensitivity. Vitamin D may improve insulin sensitivity and promote β -cell survival by directly modulating the generation and effects of cytokines⁽²⁰⁾. Vitamin D interacts with vitamin D response elements in the promoter region of cytokine genes to interfere with nuclear transcription factors implicated in cytokine generation, and its action can downregulate activation of NF κ B⁽²¹⁾.

V. DIRECT EFFECT OF VITAMIN D ON INSULIN SIGNALING

Vitamin D may directly affect insulin signaling pathways in cells. Studies have shown that vitamin D may enhance insulin signaling by increasing the expression of insulin receptor genes and other genes involved in insulin action. Vitamin D, in particular, plays an important role in biochemical and molecular reactions involved in obesity prevention through its receptor (VDR)⁽²²⁾. Vitamin D modulates insulin synthesis and decrease apoptosis in pancreatic β cells. In skeletal muscle, vitamin D is involved in the upregulation of the insulin receptor gene, improving glucose transport into the cells. VDR belongs to the nuclear receptor family participating in DNA transcription⁽²³⁾. Although the VDR acts primarily as a nuclear transcription factor, non-genomic actions of vitamin D have been postulated that involve rapid binding of 1,25(OH) $_2$ D to cytosolic and membrane VDR that activates several second messenger systems. A vitamin D response element region was identified in the promoter of the insulin receptor gene, so that vitamin D may be involved in the transcriptional control of insulin⁽²⁴⁾. In addition, Vitamin D may improve beta-cell function, which is important

for insulin secretion. Beta cells are responsible for producing and releasing insulin, and studies have suggested that vitamin D may enhance beta-cell function⁽²⁵⁾.

VI. VITAMIN D IMPROVES LIPID PROFILES

Metabolic syndrome (MS) is characterized by a combination of some risk factors such as obesity (central) associated with increased triglyceride serum levels, decreased high-density lipoprotein cholesterol levels. The dysfunction and distribution of adipose tissue has also been considered as an important factor, and the abdominal location of excess adipose tissue has been most closely associated with insulin resistance⁽¹¹⁾. The prevalence of MS has increased in recent years, which has been attributed besides to the aging of the population, to the increase in obesity rates related to lifestyle changes, such as low physical activity and poor healthy eating habits. It has been proposed that low serum 25(OH)D levels are associated with a higher risk of MS and with the different components that define MS. Vitamin D may help improve lipid profiles by increasing high-density lipoprotein (HDL) cholesterol levels and decreasing triglyceride levels. On the other hand, vitamin D supplementation may also improve the lipid profile as reported by Jamilian et al., who found a reduction of TG and very low-density lipoprotein cholesterol (LDL-C) associated with 50,000 IU vitamin D supplementation every 2 weeks for 6 months⁽⁴⁾. Imga et al. also found an improvement in HOMA-IR and LDL-C in both obese and overweight women supplemented with vitamin D3 for 6 months observing⁽⁵⁾. The beneficial effects of vitamin D on HDL-C levels have been supported by the metaanalysis performed by Ostadmohammadi et al. Although many studies suggest that vitamin D has a beneficial effect on the lipid profile, there are also studies in the opposite direction. Thus, Farrokhian et al. found no significant changes in lipid profile after vitamin D supplementation, although they reported changes in plasma malonaldehyde levels, which results from lipid peroxidation⁽²⁶⁾.

VII. ANTIOXIDANT PROPERTIES OF VITAMIN D

Oxidative stress has crucial role for proper β -cells function, glucose homeostasis, and insulin sensitivity. Hyperglycemia, dyslipidemia, lipid peroxides, and nitric oxide synthase, as well as advanced glycation end-products are involved in free radicals overproduction in the insulin resistance metabolic state⁽²⁷⁾. It is clearly recognized that oxidative stress may activate several factors contributing to the development of insulin resistance. Free radicals are highly reactive molecules that can cause damage to cells

and tissues⁽²⁸⁾. So, the relationship between vitamin D and free radicals, it's important to understand that vitamin D has antioxidant properties. Vitamin D can help combat the harmful effects of free radicals through several mechanisms include Indirect antioxidant effects where vitamin D can stimulate the production of antioxidant enzymes, such as glutathione, which help to neutralize free radicals⁽²⁹⁾. Also, modulation of inflammatory response, vitamin D has been found to possess anti-inflammatory properties, and by reducing inflammation, it indirectly reduces the production of free radicals as well as the protected effect against oxidative stress vitamin D can enhance the antioxidant defense system and help mitigate oxidative stress. Even though its primary role is not directly related to combating free radicals⁽³⁰⁾.

On the other hand, many conditions related to of insulin resistance, including PCOS, are associated with lower levels of SHBG. SHBG is a transporter protein that regulates free androgen levels. A positive correlation has been found between serum 25(OH)D and SHBG levels. In addition, data from in vitro assays with human adrenocortical cells provide convincing evidence for the suppressive effect of vitamin D on steroidogenic cells, with a consequent decrease in the levels of steroid intermediates.

VIII. CONCLUSIONS

The available literature appears to indicate a positive effect of vitamin D supplementation in metabolic syndrome patients. In this review, several findings on vitamin D and its association with disorders related to insulin resistance such as diabetes, obesity, hyperlipidemia and polycystic ovary has been analyzed. It is important to note that these conclusions are based on different research findings, and the exact mechanisms by which vitamin D improves insulin resistance may involve a combination of these factors that list above and additional pathways that are yet to be fully elucidated. Further research is needed to gain a comprehensive understanding of the underlying mechanisms involved. Overall, while the evidence is clearly evaluated, some studies suggest that vitamin D supplementation may have a beneficial effect on many diseases other than metabolic syndrome. However, more research is needed to fully understand the potential benefits of vitamin D supplementation in treating metabolic syndrome. Evam thought It is still important to consult with a healthcare provider before taking any supplements, including vitamin D.

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DECLARATIONS

Conflict of Interest The author declares no potential conflicts of interest.

ETHICAL APPROVAL

In this study there was no need of human and animal participants.

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