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Role of vitamin D in insulin resistance in obese individuals

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Abstract

Background: Vitamin D is a fat-soluble compound responsible for promoting intestinal absorption of calcium, and this, in turn, acts as a signal transmitter or activator as protein in secretory processes and release of hormones. Vitamin D receptors are distributed in various tissues of the body and involved in biochemical reactions in the pathogenesis of several diseases, such as obesity.

Objective: The aim of this article is to provide updated information on the role of vitamin D in insulin resistance in obese individuals.

Methods: It was conducted a search of articles published in PubMED, SciELO, and LILACS database, without limit for the year of publication, using the keywords "vitamin D", "insulin resistance", and "obesity".

Results: Excess adipose tissue seems to impair insulin signaling by inhibiting the phosphorylation of its receptor, resulting in insulin resistance. Studies have evidenced role of vitamin D in mechanisms involved in the pathogenesis of insulin resistance in obesity by acting in improving glycemic control both by increasing hepatic and peripheral glucose uptake and by promoting the secretion of this hormone.

Conclusions: Vitamin D exerts a protective effect in the treatment and prevention of insulin resistance in patients with obesity and protects the body against oxidative stress and chronic inflammation, contributing to glycemic control. Unfortunately, current data related to the effects of vitamin D supplementation on insulin resistance are still inconclusive.

Keywords: Vitamin D, Insulin resistance, Obesity

Background

Obesity is characterized by excessive accumulation of body fat, resulting in an imbalance between consumption and energy expenditure and is considered a risk factor for several chronic diseases to include diabetes mellitus type 2, breast cancer, and cardiovascular disease [1–3].

Excess adipose tissue promotes lipolysis, resulting in increased serum concentrations of free fatty acids (FFA), which contributes to the development of insulin resistance and subsequent reduction in glucose transport and glucose metabolism in adipose tissue and in skeletal muscle [4–6].

Extensive research has focused on the metabolic and nutritional changes involved in the pathogenesis of obesity. Vitamin D, in particular, plays an important role in biochemical and molecular reactions involved in obesity prevention through its receptor (VDR). 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 [7–9].

Recent studies have shown that excess adipose tissue reduces the bioavailability of vitamin D in patients with obesity. These patients also commonly consume vitamin-poor diets, which may also contribute to the low vitamin D levels observed [10]. In a study by Mattam and Sunny [11], patients with obesity were found to have reduced serum vitamin D levels. In

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addition, there is evidence that vitamin D, due to its liposoluble nature, appears to be stored in adipose tissue, which contributes to the manifestation of its deficiency and consequent decline of vitamin D functions in obese individuals.

Given the high prevalence of metabolic disorders in patients with obesity and the significant number of vitamin D-dependent mechanisms in the body, the purpose of our review is to highlight current information regarding the role of vitamin D in insulin resistance in patients with obesity.

Methods

The literature review was performed in the Pubmed, SciELO, and LILACS databases, with no limit of the year of publication, considering the following inclusion criteria: studies that evaluated the role of vitamin D in insulin resistance in obese individuals. The articles were selected for originality and relevance, considering the rigor and adequacy of the experimental design, the sample number, the type of physiological, and performance of measures made. The classical and recent works were preferably used.

The literature search was carried out using the following keywords: "vitamin D", "insulin resistance", and "obesity". The literature review included the following types of studies: randomized or quasi-randomized controlled clinical trials, double blind, case-control study, cross-sectional and review articles.

Metabolic and physiological aspects of vitamin D

Vitamin D is a fat-soluble compound found in both plants (vitamin D2; ergocalciferol) and animals (vitamin D3; cholecalciferol). The primary role of vitamin D is to maintain bone homeostasis [12]. The main source of vitamin D in the body is from interactions occurring in the skin upon exposure to ultraviolet B radiation emitted from the sun. Dietary sources of vitamin D contribute to approximately 20% of vitamin D in the body [13, 14].

The Institute of Medicine recommends an Estimated Average Requirement (EAR) and a Recommended Dietary Allowance (RDA) of vitamin D for individuals 19–50 years of age of 10 and 15 μg/day, respectively [15]. Dietary sources of this vitamin include fish liver oil, salmon, cod, herring, sardines, tuna, mushrooms, and egg yolk [16, 17].

As a fat-soluble vitamin, vitamin D is absorbed in the small intestine, packaged into chylomicrons, released into peripheral circulation, and then transported by a vitamin D carrier protein to target organs, including the liver. Of note, vitamin D can also be synthesized in the body ultraviolet B-induced activation of 7-dehydrocholesterol [18].

The metabolism of dietary vitamin D or vitamin D synthesized in the skin involves hydroxylation of carbon 25 by the enzyme 25-hydroxylase, forming 25-hydroxyvitamin D or calcidiol, the most abundant form of this hormone in the body [19–21]. The final stage of vitamin D production is the additional hydroxylation that occurs in the cells of the proximal convoluted tubule in the kidney, giving rise to 1,25-dihydroxyvitamin D or calcitriol, the biologically active form that exerts action through binding with the VDR [12, 22].

Several factors interfere with vitamin D synthesis and absorption. One such factor is the amount of ultraviolet B rays emitted and absorbed, which are influenced by latitude and skin pigmentation, respectively [23]. In a study by Libon et al. [24], serum vitamin D concentrations were evaluated in patients with light and dark skin pigmentation. Despite controlling for sun exposure, those with light skin pigmentation exhibited higher serum vitamin D concentrations compared to those with darker skin pigmentation. These results are similar to those reported by Chen et al. [25] and Failla et al. [26].

Another factor influencing vitamin D synthesis is the amount of 7-dehydrocholesterol concentrated in the skin. In situations where 7-dehydrocholesterol-reductase, an enzyme that converts 7-dehydrocholesterol to cholesterol, is increased, less 7-dehydrocholesterol is available for conversion into vitamin D metabolites [23].

Pre-vitamin D3, formed from UVB interaction with 7-dehydrocholesterol in the skin, exerts protection against excessive cholecalciferol production and subsequent vitamin D intoxication. Studies have shown that prolonged sun exposure isomerizes pre-vitamin D3 into two inert molecules, lumisterol and tachisterol, which impair vitamin D synthesis [20, 22].

The mechanisms involved in renal excretion of vitamin D have not been elucidated. However, evidence shows that the vitamin D binding protein, along with its ligands, has a high rate of reuptake by cells of the proximal tubules, resulting in less urinary excretion of vitamin D metabolites. Therefore, increased concentration of 25-hydroxyvitamin D in the renal tubules favors the conversion of vitamin D into its active form [20].

Another important function of vitamin D is to promote intestinal absorption of calcium by supporting the active transport of calcium to enterocytes. Vitamin D also participates in calcium mobilization in the presence of parathyroid hormone and controls the reabsorption of calcium in the distal convoluted tubule [22, 27].

Currently, the scientific community has investigated non-classic functions of vitamin D [8]. Vitamin D receptors are found in several tissues throughout the body, which provides evidence that vitamin D participates in multiple biochemical and molecular reactions and is likely involved in the pathogenesis of various diseases, such as inflammatory bowel disease, obesity, and diabetes mellitus [28, 29].

An individual's vitamin D status is measured by serum 25-hydroxyvitamin D, which has a half-life spanning of 2 to 3 weeks. However, because many factors can influence the serum concentration of 25-hydroxyvitamin D (e.g., exposure to sunlight, skin pigmentation, clothing, and certain diseases), reference values are still controversial [30].

Etiological aspects of insulin resistance in obesity

Insulin resistance is characterized by impaired glucose transport and metabolism due to reduced or no insulin production and a simultaneous increase in hepatic glucose production. Consequently, a significant rise in blood glucose concentration occurs, leading to glucose deposition in various tissues throughout the body, which, if left untreated, can result in multiple medical problems, to include death. This metabolic disorder may be partly due to changes in the signal transduction pathway of insulin [31, 32].

Several mechanisms are involved in insulin resistance: (1) impaired binding of insulin to its receptor on skeletal muscle and adipose tissue membranes; (2) downregulation of the insulin receptor gene and subsequent reduced activity and expression of insulin receptors; (3) phosphatidylinositol 3 (PI-3q) activity; (4) concentration and phosphorylation of insulin receptor substrates 1 and 2 (IRS-1 and IRS-2); and (5) translocation of glucose transporters (GLUT) [33, 34].

Several studies have analyzed the mechanisms involved in insulin resistance among patients with obesity [35, 36]. These studies have shown that excess adipose tissue promotes lipolysis and increases serum concentrations of non-esterified FFA derived from lipids, hormones, and cytokines. These processes contribute to the development of insulin resistance [6, 34].

Changes in insulin sensitivity may be explained by impaired glucose transport into skeletal muscle cells due to reduced GLUT-4 activity in patients with obesity [34, 37]. An increased concentration of FFA influences GLUT-4 expression, transcription, and translocation to the cell surface, which disrupts glucose transport into cells. An additional consequence of elevated FFA is reduced hepatic insulin clearance and increased hepatic glucose production, potentiating the effects of insulin resistance [6, 38].

It is well known that patients with obesity have chronic low-grade inflammation. Studies have shown an inverse relationship between insulin resistance and pro-inflammatory markers, such as fibrinogen, inhibitor of plasminogen activator 1 (PAI-1), and C-reactive protein (PCR) [6, 39].

Tumor necrosis factor α (TNF-α) activity requires activation of nuclear factor-κB (IKK-β), a tyrosine kinase inhibitor, which promotes serine phosphorylation and proteasomal degradation of IRS-1. When activated, IKK-β stimulates the production of other pro-inflammatory cytokines by promoting the inflammatory response and exacerbating insulin resistance [40, 41].

The increase in serum inflammatory markers present in patients with obesity may also be due to oxidative stress, which impairs enzymes involved in the insulin signal transduction pathway. Additionally, excess free radicals promote mitochondrial lesions, reducing insulin secretion by β cells in the pancreas [42]. In white adipose tissue, hypertrophy of adipocytes leads to compression of blood vessels and subsequent development of tissue hypoxia. This process compromises insulin signaling by inhibiting phosphorylation of the insulin receptor and increasing transcription of pro-inflammatory genes [43].

Furthermore, the obesity is a main cause of insulin resistance, and the pathogenic factors that induce endothelial dysfunction in the earlier stages of obesity further deteriorate insulin signaling in endothelial cells causing blunted nutritive blood flow and substrate delivery to the target tissues and thus contributing to metabolic insulin resistance [44, 45].

Vitamin D and insulin resistance in obesity

Based on available literature, there is an association between vitamin D deficiency and obesity. Studies have shown that patients with obesity often have concurrent vitamin D deficiency, with an inverse relationship between serum 25-hydroxyvitamin D levels and body weight, body mass index, waist circumference, and total body fat mass [46–48]. Giudice et al. [49] and Karatas et al. [47] observed reduced serum concentrations of 25-hydroxyvitamin D in children with obesity and in adults who are overweight or obese, respectively.

In addition, the study by Szlagatys-Sidorkiewicz et al. [50] in obese children showed that supplementing with vitamin D (1200 IU/day) for 26 weeks reduced BMI and total body fat. Similarly, Salehpour et al. [51] evaluated 77 overweight and obese women and demonstrated that vitamin D supplementation (25 μg/day) after 12 weeks resulted in a significant reduction in body fat mass.

Some factors may explain the inverse association between serum concentrations of 25-hydroxyvitamin D and body mass index, including inadequate food intake, reduced sun exposure, and decreased bioavailability of this vitamin. Studies have shown patients with obesity tend to consume foods low in vitamin D, exercise and participate in outdoor activities less frequently, and have limited exposure to sunlight [52, 53]. In obesity, vitamin D is sequestered by adipocytes due to its liposoluble nature, which reduces its bioavailability [54].

Recent research shows that vitamin D is involved in the pathogenesis of insulin resistance in obesity, by increasing the hepatic and peripheral uptake of glucose and by promoting the secretion of insulin by pancreatic

β cells [52, 54]. Regarding the role of this nutrient in the insulin secretory process, it should be noted that 1,25-dihydroxyvitamin D binds to VDR present in pancreatic β cells, favoring the release of secretory insulin granules. Vitamin D may also act indirectly in this process, as it promotes the entry of calcium into these cells, a mineral that stimulates the secretion of the hormone [55, 56].

In skeletal muscle, adipose tissue, and the liver, 1,25-dihydroxyvitamin has been shown to directly activate the transcription of the human insulin receptor gene and increase expression of the insulin receptor [57]. Furthermore, there is evidence that calcitriol increases insulin signaling in skeletal muscle and upregulate the expression of glucose transporter 4 (GLUT-4) in skeletal muscle and to stimulate GLUT-4 translocation in adipocytes [58]. Whether vitamin D deficiency influences insulin sensitivity and glucose uptake through calcium-dependent or independent mechanisms remains unknown [59].

Recent research has shown that vitamin D exerts a protective effect in the treatment and prevention of insulin resistance, which makes it a very important nutrient in patients with obesity. Vitamin D improves glycemic control in two ways: (1) by increasing hepatic and peripheral uptake of glucose and (2) by stimulating insulin secretion by pancreatic β cells via VDR signaling and promoting the entry of calcium into these cells, which stimulates insulin secretion [52, 54–56].

In addition to the above functions, vitamin D also upregulates the expression of insulin receptors, which increases the body's sensitivity to insulin and lowers blood glucose concentrations via increased transport into cells. Vitamin D also influences insulin indirectly by adjusting the influx of calcium into cells and maintaining adequate intracellular concentrations of calcium in peripheral tissues, such as adipose tissue, skeletal muscle, and kidneys [23, 60].

Vitamin D deficiency, and consequently, reduced intracellular calcium in peripheral tissues, leads to decreased insulin secretion by pancreatic β cells, impaired insulin signaling, and translocation of GLUT-4, all which contribute to the development of insulin resistance in patients with obesity [61].

Clemente-Postigo et al. [62] discovered an inverse association between serum concentrations of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and the parameters of insulin resistance, such HOMA-IR and plasma glucose levels, in patients with obesity. In a study using premenopausal women, Ferreira et al. [63] showed a negative correlation between serum vitamin D levels and parameters of insulin resistance.

Vitamin D exerts anti-oxidant effects, reducing lipid peroxidation and improving insulin sensitivity [64]. Codoner-Franch et al. [65] found high concentrations of oxidative stress markers (e.g., malondialdehyde, myeloperoxidase, and 3-nitrotyrosine) in children with concurrent obesity and vitamin D deficiency. In addition, Zhang et al. [64] found reduced activity of superoxide dismutase in children with vitamin D deficiency.

Similarly, vitamin D also exerts anti-inflammatory effects, which combats chronic inflammation and improves insulin sensitivity in patients with obesity [66]. VDR is expressed in macrophages and in cells that secrete pro-inflammatory cytokines, such as TNF-α, which require activation by NF-κB. The 1,25-dihydroxyvitamin D inhibits the IκB kinase (IKK), thus preventing the phosphorylation and degradation of IκB protein (IκB) from NF-κB. Thus, vitamin D prevents the pro-inflammatory cytokines. Consequently, secretion of these pro-inflammatory cytokines is reduced [40, 67–69]. Mutt et al. [69] demonstrated that 1,25-dihydroxyvitamin D inhibits activation of the NF-κB signaling pathway, reducing the transcription of pro-inflammatory genes.

In vitro experiments using adipose tissue fragments have shown that 1,25-dihydroxyvitamin D decreases the expression of pro-inflammatory cytokines such as monocyte-1 (MCP-1), IL-6, and IL-8 chemotactic protein [52]. Similarly, studies have shown an inverse relationship between inflammatory markers, such as C-reactive protein, serum TNF-γ and IL-6, and serum vitamin D levels [66].

Several studies have been conducted to evaluate the effect of vitamin D supplementation on inflammation in patients with obesity. However, these findings are controversial. In a study conducted by Chandler et al. [70] in overweight patients, results showed that supplementation with vitamin D (1000, 2000, and 4000 IU/day) over a 3-month period did not reduce the concentration of inflammatory biomarkers when compared to the control group. Similarly, Wamberg et al. [52] showed that vitamin D supplementation (7000 IU/day) for 26 weeks did not influence the expression of inflammatory markers in adipose tissue. Future studies are necessary for further clarification of vitamin D's influence on insulin resistance in patients with obesity.

Conclusions

Vitamin D exerts a protective effect in the treatment and prevention of insulin resistance in patients with obesity, by increasing peripheral glucose uptake and by promoting insulin secretion. Vitamin D also protects the body against oxidative stress and chronic inflammation, contributing to glycemic control. Unfortunately, current data related to the effects of vitamin D supplementation on insulin resistance are limited and inconclusive; therefore, additional studies are necessary for further clarification of vitamin D's influence on insulin resistance in patients with obesity.

Abbreviations
RDA: Recommended dietary allowance; EAR: Estimated average requirement; FFA: Free fatty acids; GLUT: Translocation of glucose transporters; HOMA-IR: Homeostatic model assessment–Insulin resistance; IκB: IκB protein; IKK: IκB kinase; IKK-β: Nuclear factor K-β; IL-6: Interleukin 6; IL-8: Interleukin 8; IRS-1: Phosphorylation of insulin receptor substrate 1; IRS-2: Phosphorylation of insulin receptor substrate 2; IU: International unit; MCP-1: Monocyte-1; PAI-1: Inhibitor of plasminogen activador 1; PCR: C-Reactive protein; PI-3q: Phosphatidylinositol 3; TNF-α: Tumornecrosis factor-α; UVB: Ultraviolet B; VDR: Vitamin D receptor

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