

The Complex Context of the Involvement of Vitamin D Deficiency in Obesity

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The prevalence of obesity is increasing and morbidity and mortality increase with it. Vitamin D plays an important role in obesity. Determining the exact relationship between obesity and vitamin D may represent a new perspective in the approach and treatment of obesity. Clarifying whether supplementation with vitamin D in overweight people can prevent obesity and whether supplementation in obese people can help weight loss are essential.

Keywords: obesity, vitamin D, treatment

Obesity is abnormal or excessive fat accumulation and is associated with a number of metabolic disorders, such as insulin resistance, hyperinsulinemia, cancer, diabetes, dyslipidemia and cardiovascular disorders. Obesity is well known as having a high degree of morbidity and mortality [1-3].

Overweight and obesity have increased over 27% over the past three decades, with over 2.1 billion people being overweight and obese [4]. It is alarming the increasing frequency of extreme forms of obesity, in these forms the life expectancy can be reduced by 6-14 years [5].

There are differences between obesity in humans and obesity in animals, the latter can exhibit obesity without the metabolic complications observed in humans [6].

Vitamin D (the active form 1,25-dihydroxyvitamin D (1,25 (OH) 2D)) is a fat-soluble hormone essential for the body, its receptors being present throughout the human body. Severe vitamin D deficiency causes osteomalacia in adults and rickets in children [7,8]. More and more research has shown that vitamin D deficiency is involved in many conditions, such as: type II diabetes, depression, cardiovascular disease, high blood pressure, dyslipidemia, cancer, etc.

Vitamin D and obesity

Even in the absence of a known causal relationship, the relationship between vitamin D, obesity but also obesity comorbidities is known and intensively studied globally.

The low serum concentrations of 25 (OH) D have a negative correlation with the body mass index and with several anthropometric or biochemical surrogates [9]. The presence of low serum vitamin D levels in obese patients may be due to the lack of outdoor physical activity, inadequate dietary intake, retention of vitamin D in adipose tissue, or a combination of these factors [10,11].

The relationship between vitamin D and obesity may be bidirectional, on the one hand obesity may cause a decrease in the level of vitamin D, on the other hand, adjusting the serum level of vitamin D may lead to weight loss in obese patients [12,13]. Pereira-Santos et al. they believed that the low level of 25 (OH) D is a possible reason behind increased adiposity by regulating parathyroid hormone and modulating adipogenesis [14]. By decreasing the level of

vitamin D, it increases the parathyroid hormone that promotes the influx of calcium into adipocytes, improves lipogenesis, causes catecholamine to induce lipolysis and leads to significant fat accumulation [15]. The active form of vitamin D - 1,25-dihydroxyvitamin D (1,25 (OH) 2D) can promote and induce apoptosis in adipocytes; by decreasing the parathyroid hormone, weight loss can occur through thermogenesis and lipolysis mediated by the sympathetic nervous system [16].

Obese people have a higher bone mineral density than underweight or normal weight people [17]. Because vitamin D deficiency is related to visceral adiposity, it could be used as a biomarker of a dysmetabolic state related to visceral adiposity. Its independent role in the development and evolution of diseases such as: cardiovascular disease, type 2 diabetes, dyslipidemia, high blood pressure, etc. cannot be excluded, due to changes in the expression of genes regulated by vitamin D receptors. In people with vitamin D deficiency, the lack of possible anti-inflammatory effects on chronic low-grade inflammation may lead to an increased risk of obesity-related metabolic disorders [18].

Obesity and the mechanism of vitamin D deficiency

There is an inversely proportional relationship between the serum level of vitamin D and the body mass index, the most likely mechanism being the volumetric dilution of vitamin D. In overweight people, the serum concentrations of vitamin D are lower because the distribution of vitamin D, in these people, is done in a larger volume [19].

Bolland et al. showed significant differences between obese and normal weight persons depending on the season, the difference in serum concentration 25(OH)D between the two categories in summer is greater and in winter it is smaller [20].

Another study by Carelli et al showed that the relationship between plasma vitamin D concentration and vitamin D concentration in subcutaneous fat compartments was similar between obese and norm-weight individuals, indicating that adipose tissue acts as a reservoir for vitamin D [21]. If the volumetric dilution is at the base of the 25(OH)D decrease in obese persons, the weight loss could normalize the 25(OH)D serum level. Mason et al raised the issue of weight loss threshold to increase serum

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25(OH)D level; significant increases in 25(OH)D of 7.7 ng/mL were recorded in weight loss greater than 15% of body weight [22].

Dermal synthesis of vitamin D does not differ from obese to normal weight individuals, however, obese individuals have low serum vitamin D levels even after supplementation or sun exposure, vitamin D (fat soluble) is accumulated and retained in adipose tissue which leads to decreased plasma levels of vitamin D in people with a large amount of adipose tissue [23].

Another mechanism may be hepatic 25-hydroxylation, which is affected in patients with non-alcoholic fatty liver disease and in hepatic steatosis, both of which are associated with metabolic syndrome and obesity [24].

It has also been shown that there is a difference in the expression of genes in vitamin D metabolizing enzymes between normal weight and obese persons, it is possible to involve the adipose tissue in the metabolism of vitamin D and does not passively store fat soluble nutrients.

Wamberg et al. found a 71% decrease in cytochrome P450 2J2 gene expression, which encodes 25-hydroxylase enzyme, and a 49% decrease in cytochrome P450 27B1 expression, which encodes 1 α -hydroxylase enzyme in subcutaneous adipose tissue in obese people [25]. No differences were observed between obese and normal-weight individuals in the expression of cytochrome P450 24A1, which encodes the enzyme responsible for 1,25(OH)₂D inactivation. After weight loss, the expression of this gene increased by 79%, suggesting the involvement of adipose tissue in the metabolism of vitamin D [25,26].

In obese people, due to low sun exposure, lack of outdoor activities and different clothing habits than normal weight, the low concentration of 25(OH)D is explained, the sun being the main source of vitamin D in 80-90% of cases [27]. In case of sun exposure, geographical and cultural differences, as well as the time of day when exposed to the sun, must also be taken into account, all of which also have an impact on vitamin D.

From a dietary point of view, in obese people diet is an essential problem, being able to contribute to a small vitamin D intake from food. Even for normal people, the total intake of vitamin D from food is a small part of what is needed. Diet may be considered a factor that is less relevant in the context of vitamin D deficiency in obesity [28,29].

Another hypothesis is that vitamin D would be involved in the pathogenesis of obesity; an increased level of parathyroid hormone, due to vitamin D deficiency, promotes lipogenesis through increased calcium flux in adipocytes [30].

Another idea to consider is that the active form of vitamin D, 1,25(OH)₂D, inhibits adipogenesis by actions modulated by vitamin D receptors [31]. Leblanc et al. have suggested that low levels of vitamin D are prone to obesity, people with vitamin D deficiency being more likely to gain weight than people with normal levels of vitamin D [32].

Vitamin D supplementation

The question arises whether administering vitamin D to obese people could help in weight loss or if it could bring other health benefits such as obesity prevention in overweight people.

A recent study reported that cholecalciferol has physiological and biochemical effect in a way that reduces metabolic abnormalities and tissue damage that may result from adiposity [33]. Cholecalciferol supports the absorption of intestinal calcium, which helps in weight loss, it also stimulates insulin receptors, being responsible for

maintaining calcium homeostasis; weight gain results from the association between cholecalciferol and insulin resistance [34,35]. Calcium supplementation, in addition to cholecalciferol, increases the inverse relationship, lowering the fat mass that has been attributed to calcium metabolism, including the calcium rich diet [36,37].

Zittermann et al. have shown that supplementation of vitamin D can significantly improve several markers of cardiovascular risk and the increase of plasma vitamin D is not associated with a significant increase in blood pressure [38]. Vitamin D supplementation has a strong impact on decreasing serum triglyceride levels in obese people due to weight loss [39].

Urinary incontinence is common in obese people, and may also be associated with a deficiency of vitamin D, in order to determine the relationship between them, more large-scale studies are needed.

1,25 (OH) ₂ D may have anti-inflammatory effects, further in vivo studies are needed to demonstrate whether increasing plasma levels of vitamin D could reduce inflammation [40]. Daily administration of 3332 IU of vitamin D for one year in obese patients during weight loss resulted in decreased TNF α but no changes in C-reactive protein or IL-6 occurred [40]. On the other hand, after daily administration of 7000 IU of vitamin D for 26 weeks, the expression of inflammatory markers in adipose tissue or circulating cytokines was not affected [40].

Studies that have looked at the effects on insulin resistance following vitamin D administration in obese people are contradictory. Vitamin D deficiency is associated with hyperglycemia, hyperinsulinemia and insulin resistance [41,42]. Von Hurst et al., following vitamin D treatment in women with insulin resistance and overweight, showed a decrease in HOMA-IR, but with no effect on glucose level, lipid profile and inflammatory markers [40]. It is still uncertain whether vitamin D administration may counteract the predisposition to develop type II diabetes.

The optimal doses and duration of vitamin D administration in obesity are not yet fully elucidated. It may be necessary to adjust the dose according to body weight, considering that the response to vitamin D supplementation is weaker in obese than in normal weight [43]. Concomitant calcium and cholecalciferol supplementation is a viable option. Moreover, for better results, a complex approach by administering cholecalciferol combined with dietary control, exercise and calcium intake seems to be the ideal option.

Conclusions

Whether obesity leads to decreased levels of vitamin D or decreased serum levels of vitamin D leads to obesity, prescribing cholecalciferol and following an effective strategy for cholecalciferol supplementation should be an imperative practice. From many aspects of the involvement and supplementation of vitamin D in obesity, certain data are lacking, which makes clear the need for thorough studies that can clarify these aspects in the future.

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