Hypovitaminosis D and Obesity – Coincidence or Consequence?

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Abstract

Vitamin D has attracted much scientific interest in recent years, mostly due to its newly described roles in metabolism regulation and cell proliferation. Along with hypovitaminosis D, the incidence of obesity has risen and has become a public health concern. The association between these two conditions is not merely coincidence and is being deeply investigated regarding its prevalence, mechanism, and even a possible causal relation. The data are still inconclusive but there is important evidence indicating that vitamin D is involved with fat accumulation, the responsible mechanism however still the principal question. The three main hypotheses are: adipose tissue sequestration, genetic modulation, such as polymorphism of the vitamin D receptor (VDR), or an organism evolutionary adaptation to cold weather. In conclusion, more evidence is needed to determine what the correct direction of this connection is and the possible therapeutic strategies of vitamin D replenishment and obesity control.

Keywords

Obesity, vitamin D, cholecalciferol, hypovitaminosis D, parathyroid hormone, polymorphism, adipocytes, supplementation

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Nowadays the number of studies involving vitamin D and its interaction with metabolism have grown and gained great exposure in the scientific literature. The main reason for this is the high incidence of its deficiency in different populations worldwide and the rising evidence of its role in the aetiology of an extensive range of diseases.[1]

Physiological Actions of Vitamin D

Apart from its well-established role in the regulation of calcium metabolism and skeletal development, vitamin D has many functions throughout the body. Important pathways were recently described based on the discovery of vitamin D receptors (VDRs) in most tissues and cells in our body and also the ability of most of them to convert it primary circulating form (25-hydroxyvitamin D) into the active form (1,25-dihydroxyvitamin).

Thus, vitamin D should be considered essential for overall health and wellbeing, especially since there is growing evidence suggesting that it has multiple functions in the regulation of cellular proliferation, differentiation, apoptosis and angiogenesis and modulation of immune responses.[2,3]

Vitamin D Sources

There are two ways by which individuals can fulfil their need of this nutrient: skin production, almost 90 % of total requirement, or diet intake. The synthesis of cholecalciferol (vitamin D3) by the skin is dependent on ultraviolet (UV) radiation from the sun, which is absorbed by the skin leading the transformation of 7-dehydrocholesterol into this form of the nutrient.[4] The amount of UV rays absorbed by the skin, and consequently of vitamin D3 produced, will depend on season, latitude, time of day, skin pigmentation, ageing and even sunscreen or clothes used.[5] Dietary sources of vitamin D are few, being represented mainly by fortified dairy products, oily fish (salmon, mackerel and sardines) and fish oil.[6] Once formed or ingested, vitamin D3 is metabolised in the liver to 25-hydroxyvitamin D3 (25(OH)D) and then in the kidney to its biologically active form, 1,25-dihydroxyvitamin D3 (1,25(OH)2D).[4]

Vitamin D Deficiency

Vitamin D deficiency is considered a clinical syndrome determined by low circulating levels of 25(OH)D: its primary and major circulating form. However, the actual levels in the blood that can define this syndrome remain unclear. Most studies considered vitamin deficiency when 25(OH)D levels are below 20 ng/ml, insufficiency as 21–29 ng/ml and sufficiency levels between 30–100 ng/ml.[7] Measures of 1,25(OH)2D are not good indicators of vitamin D status since it has a very short half-life, approximately 4 hours, and its blood levels are tightly regulated by serum levels of parathyroid hormone (PTH), calcium and phosphate. It also does not reflect vitamin D reserves, as it is frequently elevated in individuals presenting with hypovitaminosis D due to secondary hyperparathyroidism.[7]

Vitamin D and Obesity Association

Along with the increase incidence of vitamin D deficiency, the prevalence and severity of obesity has risen and has become a public health concern around the world. Associated with that, several studies have demonstrated evidence of an association between low plasma concentrations of 25-hydroxyvitamin and obesity.

The first study to notice a possible association between obesity and vitamin D was performed by Bell and colleagues in 1985. The author was intrigued by the fact that most obese individuals had higher values of serum immunoreactive PTH, which has an inverse association with

vitamin D levels, and decided to investigate whether obesity could influence the vitamin D endocrine system. Although the study was drawn from a small population, the results showed that mean serum 25-OHD was lower in obese than in non-obese subjects and attributed that to a feedback inhibition of hepatic synthesis of the metabolite by increased circulating levels of its active form, 1,25(OH)2D.[8] After this article was published, many different studies were able to reproduce these results, even in nationally representative sample such as NHANES[3,9] along with new interesting findings. Different ages groups were individually assessed, confirming this association in individuals above 65 years old[10] and children.[11] The third generation of the Framingham Study was investigated in order to determine a possible relation of vitamin D status and body composition. The results of almost 4,000 individuals confirmed the inverse relation between vitamin D and body mass index (BMI), but now independently of variation in physical activity or vitamin D intake. The authors also were able to determine a strong association between subcutaneous and specially visceral fat (evaluated by computed tomography [CT] imaging) and low values of 25(OH)D.[12]

A group of women assessed by Arunabh et al. indicated a stronger association between total body fat and low levels of vitamin D than that with BMI. The author concluded that body fat percentage is independently associated with serum levels of 25-OHD.[13] It is important, however, to keep in mind that this relation is not linear, serum 25(OH)D levels were lower both in those with low and those with high BMI values.[14] Brock and colleagues tried to determine which were the modifiable predictors of vitamin D status in a healthy population of 2,621 individuals. Obesity was significantly associated with low levels of vitamin D along with not being physically active, having low dietary vitamin D intake and season, in either men or women.[15]

The Predictive Role of Low Vitamin D Status and Obesity

The power of low levels of vitamin D to predict obesity is a controversial matter in the literature. Young and colleagues investigated the association of adiposity and vitamin D levels in ethnic groups, Hispanic and African American at baseline and 5 years later. His results showed that although vitamin D levels were inversely associated with BMI, subcutaneous adipose tissue and visceral adipose tissue at baseline, it did not predict changes in obesity in the following years.[16]

Gonzalez-Molero also investigated the relationship between vitamin D status and obesity in a population-based prospective study with follow up to 10 years. The results obtained contradict the previous study, and suggested that lower 25-hydroxyvitamin values in obese individuals could predict obesity other than be secondary to this condition.[17] The largest population analysed seeking an answer to this question was in the Hunt study, with almost two and a half thousand adults followed over 11 years. The findings suggested a prospective association with incident obesity, defined by either BMI or waist circumference. It seems that central obesity increased even faster than overall obesity.[18]

The results from Ding and colleagues pointed in a different direction in terms of adiposity and vitamin D deficiency. In his study, adiposity measures were able to predict increased incidence of vitamin D deficiency and reduced chances of recovering from it. The authors also suggested a link between inflammatory markers such as leptin, interleukin 6 (IL-6) and vitamin D deficiency in older adults. His theory is that adiposity, along with sun exposure and season, may mediate levels of vitamin D through metabolic and inflammatory mediators.[3] Gilbert Diamond and colleagues also raised interesting questions in a 3-year prospective study with a representative sample of children in Bogota, Colombia. The results confirmed the association between low vitamin D serostatus and with greater increases in BMI and also central adiposity. The author concluded that hypovitaminosis D may prospectively lead to an increase in adiposity during childhood, also implying a predictive hole of this deficit starting at a really young age.[19] Another interesting study by Crozier associated lower maternal vitamin D status with higher fat status in offspring at 4–6 years old, which would also support this conclusion at even earlier stages of life.[20]

Is it a Causal Relation? A Possible Hypothesis

Many theories have been proposed to explain the relationship between both conditions and also to understand the pathophysiological mechanisms that would link them.

Altered Behaviour and Fat Tissue Storage

The first theory is based on the a possible lack of sun exposure by obese population, which would consequently reduce the amount of vitamin D produced by the skin in those subjects. To test this possibility, Harris and colleagues conducted a cross-sectional evaluation in a healthy but older population and reported no significant differences between solar exposure and levels of 25(OH)D regardless of body fat content.[10] There is also evidence that BMI has an inverse relation with vitamin D ingestion; therefore, obese individuals consume less vitamin D orally than non-obese individuals.[21]

Other important data came from Wortsman study. In his analysis the author aimed to determine which mechanisms were responsible for the high prevalence of vitamin D deficiency in obese population. They tested two theories: an impairment in skin production/activation of vitamin D3 and a possible decreased intestinal absorption of vitamin D2. The results implied that skin production or activation of vitamin D3 does not appear to be influenced by adiposity level, since blood vitamin D3 concentrations increased in both the obese and non-obese subjects right after exposure to an identical amount of UV-B irradiation. However 24 hours after sun exposure, obese individuals had 57 % less vitamin D3 levels in their blood than in the non-obese subjects. This suggests that obese individuals have an impaired release of vitamin D3 from the skin into the circulation. The author credits this phenomenon to a higher storage of this fat-soluble nutrient in adipose tissue simply because there is more fat available for this process. The second experiment tested changes in the amount of serum 25(OH)D after a high oral ingestion of vitamin D2. The results reinforced the adipose tissue sequestration since it showed that the rise in serum vitamin D after ingestion of ergocalciferol was inversely correlated with BMI.[22] Interestingly, this association was also verified in studies evaluating the presence of storage reservoir of vitamin D in fat tissue of animals[23] and humans.[24,25]

Parathyroid Hormone Actions

Another interesting theory associates high levels of PTH with an increase of adipogenesis in individuals with low levels if vitamin D. This theory is based on the observation that obese individuals often present high levels of PTH secondary to low levels of vitamin D, independent of age, sex, season, study region and smoking.[26,27] This correlation is even stronger when body fat percentage is compared with BMI.[27] The possible mechanism by which PTH could influence and promote weight gain points to increased PTH levels, determined by low 25-OH-D levels, which promote calcium influx into the adipocytes and that this

intracellular calcium enhances lipogenesis and inhibits lipolysis leading to accumulation of fat.[28,29]

Allelic Variations in the Vitamin D Receptor Gene

Genetic modulation through polymorphisms were also thoroughly investigated in order to understand the mechanism by which low vitamin D is associated with high adiposity. Most studies rely on the analysis of genetic alterations in VDR gene, which is a high-affinity receptor that mediates most of the biological activities of 1,25(OH)2 D3. It has already been proved that deleterious alterations in the VDR gene could cause important conditions such as 1,25-dihydroxivitamin D resistant rickets; more subtle polymorphisms have a higher frequency of occurrence and may also affect the metabolism in a variety of ways.[30]

There are a few polymorphisms already described in literature that can actively influence in phenotypes regarding weigh gain and adiposity. In his study, Grundberg et al. found an association between a certain VDR genotypes and body composition in a female population. According to his research, individuals with specific kinds of VDR polymorphisms (short poly A repeat [ss] and/or absence of the linked BsmI restriction site on both alleles [BB]) present a significantly superior bodyweight and fat mass.[31] Barger-Lux found an association between VDR gene polymorphism and body size variables, particularly weight. He concluded that this polymorphism could affect bone mass through its influence on body size, more than classic nutritional mechanisms, such as intestinal absorption.[32]

Pathophysiological mechanisms of these associations are still unknown; however, a study by Kamei and colleagues discovered a direct effect of vitamin D on adipocyte differentiation and metabolism, as VDR is expressed in preadipocytes. According to his data, vitamin D is able to modulate gene expression in adipose tissue through a transcription effect, which would result in a inhibition of the differentiation of preadipocytes into adipocytes.[33] In a further investigation, Dace and colleagues were able to acknowledge that calcitriol was also able to stimulate terminal differentiation of adipocytes, even in the absence of substances formerly described as necessary to this process.[34] There is also evidence that polymorphisms in VDR could influence the circulating levels of vitamin D. Morrison and colleagues noted that the variability in circulating osteocalcin levels may reflect the allelic variation in the vitamin D receptor gene in a cohort of healthy individuals.[35] Finally, it is important to mention a remarkable discovery by Suarez and colleagues of a possible influence of VDR genotype in intra-uterine and early postnatal growth, directly or via interactions with gender-related growth regulators. In their analysis, the BB genotype could determine a greater length, weight and body surface area, whereas bb genotype could lead to smaller children.[36]

Evolutionary Theory

The last theory pupported to explain that the relation between vitamin D and obesity is based on evolutionary concepts. Foss believes that vitamin D is the cause of common obesity through a survival strategy developed by the organism during the evolutionary pathway to protect the organism from a cold climate.[37] She theorises that vitamin D originated as a photoreceptor system in primitive organisms, which were responsible to inform and defend the body against lower climates. The body would respond to lower UV radiation with reduced skin production of vitamin D that would signal the increase of fat tissue accumulation, enhancing organism protection from the cold weather by reducing heat conduction and increasing its thermogenic capacity. A higher production of vitamin D3 by the skin, induced by increased presence of sunlight in summer, would inhibit this response and promote a reduction in fat deposits.

Based on these concepts, Foss proposed a model where serum calcidiol concentration, the major circulating metabolite of vitamin D, functions as the UV-B radiation-sensitive sensor and presented by it seasonal fluctuations. This fall in its circulation is sensed in the hypothalamus inducing an increase in the bodyweight set point, which is represented by a state of energy accrual in which appetite is increased and energy expenditure reduced. The conclusion is that an improvement of vitamin D status could be a solution for the obesity epidemic and therefore more attention should be given to this matter.[37]

Possible Therapeutic Role – Vitamin D Supplementation

After investigating the causal relations and possible mechanisms linking hypovitaminosis D and obesity, some researchers started to question the possible role of vitamin D reposition. A sample of obese and overweight individuals from the Tromsø study was subjected to an intervention based on the assumption that vitamin D replacement could reverse obesity status.[14] Individuals were randomised into three groups: 40,000 IU cholecalciferol per week, 20,000 IU cholecalciferol per week or placebo, along with calcium supplement, and evaluated every 3 months for a year. The outcome was surprising – they observed a sustained increase in serum 25(OH)D levels along with a reduction in serum PTH in both groups but no reduction in bodyweight, not even in those with initial low serum 25(OH)D levels.[38] Trivedi also found no significant difference in bodyweight after 5 years of oral supplementation of 100,000 IU vitamin D3, every 4 months, in an older but healthy population.[39]

Salehpour and colleagues likewise tested the effect of 25 µg (1, 000 UI)/day of cholecalciferol on body composition of a group of healthy overweight and obese women over 12 weeks. Although there were significant differences in levels of Serum 25(OH)D and serum PTH concentrations in both groups, there was no significant alteration in weight loss or even waist circumference. They noticed, however, a modest fat mass reduction associated with the significant increase of 25(OH)D levels and the significant decrease of PTH levels.[40] Roseblum and colleagues showed, in a 16-week study of overweight and obese individuals, a significant loss in visceral fat percentage and volume.[41]

Zhu evaluated the effect of vitamin D + calcium supplementation associated to hypocaloric diet over 12 weeks in obese and overweight individuals who were considered very-low calcium consumers. The results agreed with the previous ones mentioned, indicating that vitamin D + calcium supplementation can promote greater body fat and visceral fat loss.[42] Zittermann and colleagues also evaluated the effect of vitamin D supplementation along with a weight-loss programme in a longitudinal study with a follow up of 1 year. The results, nevertheless, indicated no beneficial effects of the supplementation in weight loss.[43]

Going in the opposite direction, Ortega and colleagues analysed the repercussion of vitamin D status on the loss of body fat in young overweight/obese women following two slightly hypocaloric diets, but without supplements. Sixty individuals were randomly assigned to two different diets but both with 20 % less energy than the established requirement. The results were noteworthy revealing that individuals with a higher vitamin D status responded better to hypocaloric diets,

with a greater loss of fat mass. The author suggests that a restoring vitamin D levels could be an important strategy for weight loss diets.[44] The available data are still inconclusive when it comes to the impact of vitamin D supplementation and weight loss; however, it appears that it could have a greater influence in body fat distribution, especially with the reduction of visceral fat. The heterogeneity of the published studies also contributes to the lack of comparable results.[45]

Dosage Adequacy

The right amount of oral vitamin D intake to maintain an adequate status is also a matter of discussion in different studies. According to Zittermann's review, there is currently no recommended intake level for vitamin D. The available adequate intake values are crude estimates in order to prevent vitamin D-dependent diseases such as rickets and osteomalacia.[46] Moreover, there is great evidence that obese individuals are more susceptible to vitamin D insufficiency and therefore may require higher doses of vitamin supplementation to achieve adequate levels.

Lee et al. investigated if an increase in serum vitamin D is BMI dependent and therefore the supplementation dosage should be modified depending on obesity degree. His data suggested that a larger dose of vitamin D supplementation is required in the obese population for repletion of this nutrient deficiency compared with normal-weight individuals. Larger doses of vitamin D supplementation were proved also to increased conversion of 25(OH) D to 1.25(OH)2 D.[47] In their analysis, Dong and colleagues, found that black youth with greater fat mass may also require a higher dosage of vitamin D in order to achieve similar results in nutrient repletion.[48] This evidence suggests that more studies are needed to determine the exact amount of vitamin D supplementation able to overcome the deficiency in obese population. In light of this problem, Holik et al. developed a guideline for the evaluation, treatment, and prevention of vitamin D deficiency. They recommend screening for 25(OH)D levels in all at-risk individuals, and defined deficiency for levels below 20 ng/ml. For obese individuals the recommendation is an intake of two or three times more vitamin than their age group reference, and also to maintain levels of more than 30 ng/ml.[7]

Conclusion

The relation between obesity and vitamin D is complex and filled with unknown details and mechanism. And, although there is a lot of evidence available about its actions in obesity, there are still no consensus regarding preventative actions of supplementation and possible therapeutic roles of this nutrient. Based on this review we can affirm that there is an inverse association between body fat content and vitamin D but there is still not enough evidence to confirm if this relation is causal or collinear. More evidence is needed to determine what is the correct direction of this connection and, based on that answer, the possible therapeutic strategies of vitamin D replenishment and obesity control. ■

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