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Vitamin D Status in Obesity: Relation with Expression of Vitamin D Receptor and Vitamin D Hydroxylation Enzymes in Subcutaneous and Visceral Adipose Tissue

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Abstract

Currently and worldwide, a high prevalence of obesity, obesity-associated metabolic dysfunction, and vitamin D (VD) deficiency occurs. Besides participating in bone mineralization and calcium homeostasis, VD has other major functional roles. The vitamin D receptor (VDR) signaling pathway is crucial for the proper functioning of adipose tissue (AT). AT is a reservoir for VD and can activate/inactivate VD by hydroxylation. Subcutaneous and visceral AT (SAT, VAT) have different and prime roles in metabolic regulation/dysfunction. A search was done on PubMed/Medline, Web of Science, and Scopus databases using the following keywords: vitamin D, vitamin D receptor, hydroxylases, subcutaneous adipose tissue, visceral adipose tissue, obesity, and metabolic dysfunction. Our chapter focuses on human studies on VD status and expression of VDR and VD activation/inactivation enzymes in SAT and VAT in an obese environment.

Keywords: obesity, adiposity measures, visceral adipose tissue, subcutaneous adipose tissue, vitamin D, vitamin D receptor, vitamin D hydroxylation

1. Introduction

Obesity is defined as an excess amount of body fat that may impair health [1] and has been strongly associated with chronic low-grade or metabolic inflammation characterized by the activation of inflammatory signaling pathways and abnormal secretion of a large set of immune response mediators and several bioactive proteins [2, 3] known as adipokines [4] and a deficit of mediators responsible for the resolution of this process [5]. Within the adipose tissue (AT),

other cells are also present including preadipocytes, mast cells, and macrophages, which also contribute to this inflammatory environment. Currently and worldwide, obesity is the fifth greatest risk factor for mortality [6], and it is associated with vitamin D deficiency (VDD) [7].

Vitamin D (VD) is essential for the development and maintenance of bone tissue, as well as for normal homeostasis of calcium and phosphorus [8]. Moreover, VD has other major functional roles; it is related to differentiation, cell proliferation, and hormone secretion. It is an important nutrient with crucial role in obesity onset (AT) and in the comorbidities associated with the chronic inflammation [9].

An estimated 80–90% of VD from the human body originates from skin synthesis, with sunlight activation, while the rest is supplied through supplements or food [10]. VD status is measured by means of the plasma levels of 25-hydroxyvitamin D [25(OH)D] or calcidiol, the dominant circulating form and the best indicator of VD status [11]. The action of 1,25(OH)₂D, active form of VD [12], is mediated through the vitamin D receptor (VDR), a member of the nuclear receptor superfamily, which regulates the transcription of many target genes [13].

The VDR signaling pathway is crucial for the proper functioning of AT that is called an active endocrine organ, which plays an important role in fat storage and in the production and secretion of adipokines [14, 15]; is a reservoir for VD; and, besides, can activate/inactivate it by hydroxylation. VD and VDR are implicated in preadipocyte differentiation into adipocytes [16].

Major differences between subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) were shown in the expression of VD-metabolizing enzymes. The expression of the VDR, 25-hydroxyvitamin D 1 α -hydroxylase (CYP27B1) genes, and 24-hydroxylase enzymes has been shown in human adipocytes [17].

In line, our chapter will focus on VD status and expression of VDR and VD hydroxylase enzymes in SAT and VAT in an obese environment.

2. Vitamin D, VDR, and hydroxylase enzymes on adipose tissue

2.1. Vitamin D

VD is a hormone mainly described for its role as a regulator of phosphate and calcium homeostasis [18, 19], therefore playing an important part in bone metabolism, and seems to have some anti-inflammatory and immune-modulating properties. This micronutrient can be obtained through animal (VD₃, cholecalciferol) or plant (VD₂, ergocalciferol) food sources. However, vitamin D₃ is the only form that is found naturally in human subjects and other animals. Although the main source of vitamin D₃ is through endogenous synthesis in the skin, the vitamin can also be obtained from the diet, and this is important for those who have limited exposure to the sun [20].

VD₃ is produced endogenously in the skin after UVB irradiation, between 290 and 315 nm, present for limited number of hours also varying with respect to latitude and reason. VD₃ is

formed from the precursor 7-dehydrocholesterol to give pre-VD₃ and further is released into the circulation [21]. Vitamin D₃, whether derived from sunlight or the diet, enters the circulation bound to vitamin D-binding protein (DBP) and is transported to the liver. VD₃ is hydroxylated in the liver to 25(OH)D, the major circulating vitamin D metabolite; it has a relatively long half-life (15 days) but, however, is an inactive form. The Institute of Medicine proposed that serum 25(OH)D concentrations below 50 nmol/l or 20 ng/ml should be considered to represent the deficiency of this nutrient [22]. 25(OH)D is then further hydroxylated by 1 α -hydroxylase enzyme (gene: CYP27B1), and this occurs primarily in the kidney to produce 1,25(OH)₂D, the biologically active form of VD [23, 24].

In relation of signaling of VD in AT, 25(OH)D can promote the differentiation of human adipocytes, most likely via its activation to 1,25(OH)₂D [25]. The local metabolism of VD in AT may regulate the conversion of preadipocytes to adipocytes and later support the healthy remodeling of human AT. Also, 1,25(OH)₂D may promote the differentiation of human preadipocytes by maintaining a high expression level of key adipogenic transcription factors, like C/EBP α and PPAR γ gene expression, the two master regulators of adipogenesis that were increased during the late phase of differentiation [26]. Besides, 1,25-dihydroxyvitamin D modulates adipogenesis through VDR-dependent inhibition of critical molecular components of it such as PPAR γ [27].

The emerging role of VD in immune regulation suggests that this endocrine factor can modulate the inflammatory responses in AT. 1,25(OH)₂D displayed an anti-inflammatory effect and its ability to improve the insulin-stimulated uptake of glucose, as well as enhance and improve the function of pancreatic β -cell [28]. To strongly support the anti-inflammatory effect of 1,25(OH)₂D in adipocytes, the improvement of pro-inflammatory status and glucose uptake in adipocytes under 1,25(OH)₂D effect suggest that low-grade inflammation could be linked to VDD [29].

The 1,25(OH)₂D significantly reduced the basal release of MCP-1, IL-8, and IL-6 from preadipocytes (MCP-1 is produced by macrophages which increase further macrophage infiltration into AT [30], and circulating levels of IL-8 are increased in obesity). It should also be pointed out that since adipocytes store VD, adipocytes and monocytes/macrophages are able to locally convert 25(OH)D to 1,25(OH)₂D [31, 32], and the concentrations of VD within AT could be higher than implied by the plasma levels. Vitamin D₃ may protect against AT inflammation in obesity by disrupting the deleterious cycle of macrophage recruitment [33].

Lower 25(OH)D is associated with greater regional adiposity; this is stronger in VAT than SAT and significant across the spectrum of body size [34]. VD has been reported to act as an acute phase reactant as a consequence of such an inflammatory response occurs in obesity, which can suppress the concentration of 25(OH)D [35].

2.2. Vitamin D receptor

The human VDR is a 50- to 60-kDa molecule, a member of the nuclear receptor superfamily that is the only nuclear receptor that binds to 1,25(OH)₂D with high affinity and specificity. VDR forms a heterodimer with the retinoid X receptor acting as a transcription factor that binds

to VD response elements in the promoter region of target genes [36]. VDR expression has been identified in most human tissues, including in osteoblasts, skin keratinocytes, macrophages, smooth muscle, pancreatic β -cells and epithelial cells [37, 38], and it is also highly expressed in adipocytes.

The action of $1,25(\text{OH})_2\text{D}$ is mediated through the VDR, which regulates the transcription of many target genes [13]. There are more than 1000 genes that are directly or indirectly regulated by $1,25(\text{OH})_2\text{D}$ and involved in various physiological processes such as cell proliferation, differentiation, apoptosis, and angiogenesis [38].

VDR expression is increased in obese, which has more VAT than lean subjects, but the physiological relevance of this upregulation has not yet been elucidated. VAT VDR gene expression correlated positively with body mass index (BMI) [39]. The ubiquitous expression of VDR may underlie the diverse effects of VD and provide a mechanistic basis for the link between VDD and a number of disorders that are linked with obesity like certain types of cancer, inflammatory bowel disease, cardiovascular diseases (CVD), diabetes (type 1 and type 2), and the metabolic syndrome [40–42].

Expanding to another approach, there are associations of VDR variants with the more metabolically active fat, VAT, which is more closely tied to the metabolic consequences of adiposity. Association of VDR SNP rs4,328,262 with VAT supports the notion that the VDR gene is likely to be related to the development of obesity and obesity-related outcomes [43]. Polymorphisms in the VDR gene might play a role in regulating AT activity body fatness and susceptibility to adiposity among African Americans, albeit genetic factors that contribute to adiposity are certainly more complex than to be explained totally by variations in a single gene.

2.3. Hydroxylase enzymes

The formation, activation, and catabolism of $25(\text{OH})\text{D}$ are complex processes, which involve mitochondrial and microsomal cytochrome P450 enzymes. In humans, four cytochrome P450 enzymes, CYP2R1, CYP3A4, CYP27A1, and CYP2J2, [44–47] possess 25-hydroxylase activity, with CYP2R1 being the most specific. Hydroxylation in the 1α -position is effected by the mitochondrial CYP27B1. This process was classically located to the kidney, but recently, extrarenal 1α -hydroxylase activity has been described in several other tissues [48]. $1,25(\text{OH})_2\text{D}$ stimulates its own degradation by induction of the 24-hydroxylase (CYP24A1), which catabolizes $25(\text{OH})\text{D}$ and $1,25(\text{OH})_2\text{D}$ to calcitroic acid and other inactive metabolites [49].

2.3.1. 25-Hydroxylation

Various enzymes may be associated with the first hydroxylation of $25(\text{OH})\text{D}$, but CYP2R1 seems to be the key to this hydroxylation [50]. In humans, other cytochromes P450 such as CYP3A4, CYP27A1, and CYP2J2 show activity of 25-hydroxylase to vitamin D molecules but less efficient. CYP2J3, CYP2D25, and CYP2C11 also show activity of 25-hydroxylase but are only expressed in male pigs and rats, respectively [51]. 25-Hydroxylation appears to be functional in AT. Interestingly, in human AT, biopsies have confirmed the expression of

CYP27A1, CYP2R1, and CYP2J2, suggesting that human AT and adipocytes are able to convert vitamin D₃ into 25(OH)D.

2.3.2. 1 α -Hydroxylation

25(OH)D is then secreted into the circulation or directed to 1 α -hydroxylase CYP27B1 mitochondria to be metabolized to 1,25(OH)₂D. CYP27B1 is the key enzyme 1 α -hydroxylation, and its activity is regulated by the parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), calcium, and phosphorus and self-regulated by 1,25(OH)₂D via negative feedback mechanism [18]. CYP27B1 mRNA, which encodes the 1 α -hydroxylase that converts 25(OH)D to the biologically active 1,25(OH)₂D, was present at significant levels in SAT and VAT. This gene was mainly expressed in the stromal vascular fraction of human AT that contains preadipocytes, macrophages, and endothelial cells. The expression of CYP27B1 has also been detected in adipocytes of murine [17] and human AT biopsies [52].

2.3.3. 24-Hydroxylation

Vitamin D 24-hydroxylase (CYP24A1) is responsible for the inactivation of 1,25(OH)₂D. This inactivation is self-regulated, from 1,25(OH)₂D induces the expression of CYP24A1 which converts 25(OH)D in 1,25(OH)₂D within the less active metabolites (24,25(OH)₂D and 1,24,25(OH)₃D), which are later catabolized into inactive calcitroic acid [53]. In AT, the expression of CYP24A1 has been detected in murine and human adipocytes. Additionally, levels of CYP24A1 mRNA are strongly induced by incubation of 1,25(OH)₂D.

The expression of 25-hydroxyvitamin D 1 α -hydroxylase (CYP27B1) genes and 24-hydroxylase enzyme has been shown in human adipocytes [17]. The CYP24 gene, which encodes the enzyme catalyzing 1,25(OH)₂D, was also found to be expressed by human adipocytes and preadipocytes [31, 54]. Recently, a low expression of CYP27B1 gene in SAT of obese individuals has been shown [52]; this finding corroborates the ability of AT to metabolize VD locally. One of the main mechanisms by which this vitamin may act in human AT is via the expression of VD-metabolizing enzymes such as 25-hydroxylase CYP2J2, CYP27B1, and CYP24 [55]. This capacity to metabolize VD locally was demonstrated when, after weight loss in obese subjects, plasma 25(OH)D increased and expression levels of 25-hydroxylase CYP2J2 and 1 α -hydroxylase CYP27B1 declined in the SAT of these subjects. So, a dynamic alteration may occur in AT during weight loss and obesity.

In the SAT of the obese individuals have a lower expression of one of the enzymes responsible for 25-hydroxylation of VD (CYP2J2), as well as a tendency toward a decreased expression of the 1 α -hydroxylase, 25-hydroxylation and the 1 α -hydroxylation in SAT are impaired in obesity AT expresses the enzymes for both the formation of 25(OH)D and of 1,25(OH)₂D, and for degradation of VD. To explain an altered VD metabolism in obesity, major differences between SAT and VAT in the expression of VD-metabolizing enzymes occur with difference in spreading between lean and obese subjects [52]. The expression of CYP27A1 is more pronounced in VAT than in SAT, without differences between lean and obese women, while the expression of

CYP2J2 is more prominent in SAT than in VAT in lean women. So, these findings lead to a compromised of 25-hydroxylation in SAT in obese, taken by a lower expression of the CYP2J2.

3. Mechanisms suggested for VDD in obesity

Several studies have shown the relationship between obesity and inadequacy of VD [56–58]. Evidence suggests that one of the VDDs in subjects with obesity may be connected to storage of VD in the adipocytes, reducing its bioavailability and activating the hypothalamus to develop a cascade of reactions that result in increased feelings of hunger and decreased energy expenditure [59]. Low serum of 25(OH)D concentrations is found to be inversely correlated with measures of obesity, including body mass index (BMI) ($\geq 30\text{kg/m}^2$), fat mass, and WC [60, 61]. A bidirectional genetic study has suggested that higher BMI chiefly to lower 25(OH)D; each unit increase in BMI is being associated with 1.15% lower concentration of 25(OH)D, after adjusting for age, sex, laboratory collection, and month of measurement [62]. The relationship between obesity and 1,25(OH)₂D is less clear, and this is probably due to the dynamic nature of the production and regulation of the active hormone. However, the study in vitro showed that 1,25(OH)₂D acts as a potent inhibitor of leptin secretion in a culture of human adipocytes [63].

Extensive evidence has demonstrated that adipocytes become enlarged and dysregulated the following weight gain, which subsequently produces an imbalance in the inflammatory profile of AT. So, obesity is commonly linked to an upregulation of pro-inflammatory molecules and downregulation of anti-inflammatory molecules [64]. Individuals with both high SAT and high VAT have an approximately threefold prevalence of VDD compared with those with both low SAT and low VAT [34]. A predominant effect of VD on macrophages could explain the differences observed in relations of VD response in VAT versus SAT. It is observed a greater macrophage infiltration of VAT when compared with SAT in individuals with obesity. In contrast, inflammatory markers in AT strongly correlate with macrophage infiltration [65], and many metabolic differences could potentially explain the different VD-induced anti-inflammatory response observed between these two types of AT, including the number of cells expressing the VDR [52]. Because ATs of obese are infiltrated with macrophages, it seems likely that macrophages also contribute to the local activation of VD. Because SAT and BMI are closely correlated, it is possible that most of the association between SAT and 25(OH)D is attributable to the difference in body size that is seized by BMI. It is observed that lower 25(OH)D was associated with greater regional adiposity.

In fact, the basis of low concentration in subjects with obesity is not totally known but could be the result of various mechanisms. There are five suggested mechanisms that are most commonly cited within the literature which may explain a low VD status in obesity:

- *Obese individuals have reduced sun exposure compared with lean subjects.*
- *Low 1,25(OH)₂D inhibits adipogenesis.*

- *Negative feedback control.*
- *Vitamin D is sequestered within adipose tissue.*
- *Lower 25(OH)D concentration is just due to volumetric dilution.*

3.1. Reduced sun exposure

Obese individuals reduce their exposure to sunlight, reportedly have a limited mobility, avoid performing outdoor activities, and/or use clothes that cover more of the body [56], which limit exposure to the sun and, consequently, cutaneous VD synthesis. However, in a study based on the Framingham cohort, which evaluated the association between obesity and VD, it was reported that after adjustments for practicing outdoor physical activities, this theory was insufficient to explain the relationship between obesity and VDD [34]. In addition, the study indicates that daily exposure to 0.5 standard erythemal dose (SED) between 11:00 and 13:00h, using typical summer clothing, was not enough to achieve the state suitable of VD in the late summer [66]. Until now, it is still unclear which VD supplementation dose corresponds to the amount of UVB radiation exposed, in regard to efficiency to increase serum concentrations of 25(OH)D and as little establishing a standard exposure solar time daily necessary to achieve an adequate state of VD [67].

3.2. Low 1.25(OH)₂D inhibits adipogenesis

Some experimental data have suggested that VDD can favor greater adiposity by promoting increased PTH hormone levels and greater inflow of calcium into adipocytes, so increasing lipogenesis [68]. Evidence suggests that low 1.25(OH)₂D inhibits adipogenesis through actions modulated by vitamin D-dependent receptors [69]. Thus, depletion of vitamin D can lead to excessive differentiation of preadipocytes to adipocytes.

3.3. Negative feedback control

Excess AT impairs the VD status from activating energy expenditure. In this mechanism, the leptin stimulates osteocytic FGF23, inhibits renal synthesis of 1 α -hydroxylase, and consequently impairs the production of 1,25 (OH)₂D, creating a negative feedback mechanism [70].

3.4. Sequestration in adipose tissue

Wortsman et al. [71] published the first study to provide strong convincing evidence that VD (as a fat-soluble vitamin) may become sequestered within AT. In their study, the concentration of circulating cholecalciferol was similar between obese and lean groups at baseline, but the obese group had a significantly reduced response to the UVB intervention, resulting in a 57% lower serum cholecalciferol concentration postintervention, compared with the control group (lean). This suggested that the limitation in the obese group was the bioavailability of the synthesized cholecalciferol in circulation [71]. This sequestration theory is probably the most supported in the literature.

3.5. Volumetric dilution

Most recently, Drincic et al. [72] showed that body weight and body fat are inversely correlated with 25(OH)D levels across the spectrum of body weight ranging from normal to obese. This inverse association is related to the greater volume of distribution for both VD_3 and 25(OH)D in tissue mass. They suggested that simple volumetric dilution is the most thrifty explanation for the low VD status in obesity. A hyperbolic model best explains the lower 25(OH)D values in obesity, and when serum 25(OH)D values was adjusted for body weight, difference between obese and normal subjects disappeared. These authors went on to recommend that the VD dosing for treatment of VDD in obesity should be based on body weight, for example, “one size does not fit all” [72].

Overall, although these are the five most commonly suggested mechanisms, the latter two theories have more robust evidences available. The strong evidence presented for the sequestration and volumetric dilution hypotheses, and more importantly, a lack of contradictory evidence for either, suggest that they are the most probable, independently or in combination, to explain the low VD status widely reported in obesity.

4. Conclusions

The prevalence of obesity and VDD is growing exponentially in recent decades, and several studies have been conducted worldwide, particularly, the signs of VDR and hydroxylase enzymes in AT (SAT and VAT). VD is a nutrient with important role in the genesis of obesity and also in diseases associated with chronic inflammation. It features an anti-inflammatory effect in AT, anti-adipogenic activity, exerts immunoregulatory effect, and has the capacity to limit the expression of inflammatory markers in AT. Scientific evidences suggest that AT is a target for VD action, as CYP27B1 and VDR genes that are expressed by adipocytes. All evidence suggests that 25(OH)D, 1,25(OH)₂D, and VDR are involved in the AT, through the endocrine system as well as autocrine/paracrine actions of VD.

Based on news researches, there is a hypothesis that AT is not only a stock of VD but also has a dynamic ability to activation and deactivation of this vitamin in obesity. Low VD status in obesity may have implications for AT biology based on recent data from different research groups which are converging to highlight the impacts of VD on AT/adipocyte biology. Therefore, some key points have yet to be elucidated in relation to VD metabolism and its regulation on AT, especially in obese environment.

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