Vitamin D modulates adipose tissue biology: possible consequences for obesity?

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Cross-sectional studies depict an inverse relationship between vitamin D (VD) status reflected by plasma 25-hydroxy-vitamin D and obesity. Furthermore, recent studies in vitro and in animal models tend to demonstrate an impact of VD and VD receptor on adipose tissue and adipocyte biology, pointing to at least a part-causal role of VD insufficiency in obesity and associated physiopathological disorders such as adipose tissue inflammation and subsequent insulin resistance. However, clinical and genetic studies are far less convincing, with highly contrasted results ruling out solid conclusions for the moment. Nevertheless, prospective studies provide interesting data supporting the hypothesis of a preventive role of VD in onset of obesity. The aim of this review is to summarise the available data on relationships between VD, adipose tissue/adipocyte physiology, and obesity in order to reveal the next key points that need to be addressed before we can gain deeper insight into the controversial VD–obesity relationship.

Adipose tissue: Vitamin D: Obesity: Inflammation: Adipocytes: Nutrients: Nutrition

Vitamin D: a brief overview

Vitamin D (VD; calciferol) is a hormone mainly described for its role as a regulator of phosphate and calcium homeostasis(1). It can be obtained through animal (VD3, cholecalciferol) or plant (VD2, ergocalciferol) food sources. Only a few foodstuffs contain significant amounts of VD, the main sources being fish liver oils, fatty fish (sardines, herring and mackerel) and egg yolk(2,3), but small quantities are also found in fortified milk, orange juice, bread and cereals. Alternatively, VD3 is produced endogenously in the skin after UVB irradiation from the precursor 7-dehydrocholesterol to give pre-VD3, which is further isomerised to VD3 before being released into the circulation(4). Classical estimates have assigned a majority (70–90 %) of VD supply to dermal synthesis, but a recent paper revised this figure down to just 10–25 % of VD supply(5) and posited that dietary intake of 25-hydroxy-vitamin D (25(OH)D) is a significant contributor to total VD input.

Adipose tissue is a major storage site for vitamin D

Despite limited data, it is widely accepted that adipose tissue is a reservoir for VD in human subjects and rats(6–10). Interestingly, visceral fat was found to contain 20 % more VD than subcutaneous fat(11). Heaney et al.(12) calculated that 65 % of total VD in the body is in the form of D3, for which adipose tissue and skeletal muscle appear to be the main body stores (accounting for 73 and 16 %, respectively). Regarding 25(OH)D, 34 % of it is found in adipose tissue, 30 % in serum and 20 % in skeletal muscle. However, 25(OH)D was recently
detected in human subcutaneous adipose tissue\(^{(13)}\). Fat tissue may thus contain about 60 % of total body VD, but the amount of VD present in fat tissue varies strongly between individuals and is not correlated to serum 25\((\text{OH})\)D levels\(^{(14)}\), whereas 25\((\text{OH})\)D adipose tissue content seems to be correlated to 25\((\text{OH})\)D plasma levels\(^{(13)}\). Other factors such as VD status and amount of intake can also influence adipose tissue storage. Indeed, it was calculated that for low VD intakes and when serum 25\((\text{OH})\)D concentration is below 88 nM/l, almost all VD is converted to 25\((\text{OH})\)D in the liver with very little deposited in tissues\(^{(14)}\), indicating that low 25\((\text{OH})\)D status is associated with limited tissue stores as well.

A recent pilot study using time-of-flight secondary ion mass spectrometry confirmed that both VD and 25\((\text{OH})\)D were present in human adipose tissue, and also reported for the first time that 1,25-dihydroxy-vitamin D (1,25\((\text{OH})\)\(_2\)D) was also detectable in fat tissue\(^{(15)}\). This pilot study also suggested that all these molecules were located in adipocyte lipid droplets and that VD and 25\((\text{OH})\)D concentrations in adipose tissue were lower in obese than lean subjects, although this last observation was only generated with a very limited number of samples\(^{(15)}\).

**Parallel between systemic vitamin D metabolism and adipose tissue metabolism**

**Uptake of vitamin D**

VD from food is partially absorbed in the distal part of the small intestine, in emulsion with bile salts\(^{(16)}\). Its intestinal absorption occurs not only by passive diffusion but also via at least two cholesterol carriers\(^{(17,18)}\). VD and its metabolites are majorly transported in the plasma bound to vitamin D-binding protein (DBP), a globulin produced in the liver\(^{(19)}\), but also to albumin, LDL and chylomicrons for dietary VD\(^{(20)}\). Plasma DBP is in large excess compared with VD and metabolites, thus leaving only a very limited amount of circulating unbound VD and metabolites\(^{(21)}\). Interestingly, only the unbound part of VD is considered biologically active and able to diffuse in any target cells\(^{(21)}\), thus leading to the free-hormone hypothesis\(^{(22)}\). Indeed, despite having low plasma levels of the different forms of VD compared with wild-type animals, Dbp-null mice do not show any signs of disrupted calcium homeostasis, suggesting that free VD levels can cover the needs of physiological functions as long as diet is VD-sufficient\(^{(22)}\). Subsequent work showed that kidney content of 1,25\((\text{OH})\)\(_2\)D was not different from that of wild-type animals\(^{(24)}\). Taken together, these data suggest that tissues may uptake VD and metabolites from the free pool through a DBP-independent mechanism.

The molecular mechanisms involved in VD uptake/secretion by adipose tissue have not yet been investigated but may well involve the megalin/cubulin pathway (described later) as suggested by Abboud et al.\(^{(25)}\) and/or cholesterol transporters as described in the intestine\(^{(17)}\) or for other lipophilic micronutrients in adipose tissue\(^{(26)}\).
via the activation of a gene reporter system and through the identification of radiolabelled 1,25(OH)₂D derived from radiolabelled 25(OH)D (43). The production of 1,25(OH)₂D from 25(OH)D was then confirmed by Ching et al. (44) and Nimitphong et al. (45). CYP27B1 expression has also been detected in murine adipocytes (43) and in human adipose tissue biopsies (38).

24-hydroxylation

Finally, vitamin D 24-hydroxylase (CYP24A1) is in charge of inactivating 1,25(OH)₂D. This inactivation is self-regulated, since 1,25(OH)₂D induces the expression of CYP24A1 that converts 25(OH)D and 1,25(OH)₂D into less-active metabolites (e.g. 24,25(OH)₂D and 1,24,25(OH)₃D), which are further catabolised into inactive calcitriolic acid (40).

In adipose tissue, CYP24A1 expression has been detected in murine and human adipocytes (43, 45). In addition, the mRNA levels of CYP24A1 are strongly increased by 1,25(OH)₂D incubation (43, 44). CYP24A1 expression has also been confirmed in human adipose tissue biopsies (38).

Vitamin D signalling

Even if few VD receptor (VDR)-independent effects of 1,25(OH)₂D have been documented (46), most biological activities of VD are mediated by the VDR, a member of the nuclear receptor superfamily that is the only nuclear receptor that binds 1,25(OH)₂D with high affinity (47, 48). VDR expression has been demonstrated in almost all human tissues (49), which means that all cells are potential targets of 1,25(OH)₂D action. The VDR–1,25(OH)₂D complex is associated with the retinoid X receptor (50) and the retinoid X receptor–VDR–1,25(OH)₂D complex binds to the DNA of sites called VDR response elements in the promoter region of genes whose expression is either activated or repressed (47). There are more than 1000 genes that are directly or indirectly regulated by 1,25(OH)₂D and involved in various physiological processes such as cell proliferation, differentiation, apoptosis and angiogenesis (51).

The presence of VDR in adipose tissue was first reported in the early 1990s (52) and has since been widely confirmed. Interestingly, it was recently found that VDR expression is increased in obese compared with lean subjects (53), but the physiological relevance of this up-regulation has not yet been elucidated.

Another VD-dependent signalling pathway has been described that involves ERp57 (also known as GRP58 or 1,25D3-MARRS), a protein disulfide isomerase involved in stress response (54) that mediates rapid cellular responses (i.e. within seconds or minutes) to 1,25(OH)₂D stimulation (55, 56). ERp57–1,25(OH)₂D complexes are internalised, which opens the possibility that ERp57 might also participate in 1,25(OH)₂D intracellular trafficking, especially since ERp57 has been found to participate in nuclear complexes, including heat-shock protein 70, one of the human intracellular DBP. However, it is not yet known whether this signalling pathway is active in other tissues, particularly adipose tissue.

Taken together, these data demonstrate that on top of being a major storage site for VD, adipose tissue also expresses enzymes involved in VD metabolism and signalling, which points to the hypothesis that adipose tissue could be a target tissue that is also able to synthesise 25(OH)D and 1,25(OH)₂D that could be locally active via paracrine, autocrine or even intracrine processes (57). The regulation of this local metabolism has never been studied but certainly warrants future investigation. Nevertheless, there is increasing evidence of the impact of VD and its active metabolites on adipose tissue, notably in terms of adipogenesis control, adipokine expression and a host of other metabolic regulations.

In vitro and in vivo effects of vitamin D on adipose tissue and adipocyte biology

Regulation of adipogenesis

Many studies have examined the role of 1,25(OH)₂D in the proliferation and differentiation of murine 3T3-L1 pre-adipocytes (52, 58–61). Low 1,25(OH)₂D concentrations were associated with an inhibition of adipogenesis and a reduction of TAG accumulation in 3T3-L1 cells, even if the opposite effects, i.e. induction of adipogenesis, have also been depicted in this cellular model (62). The mechanism governing these effects implies 1,25(OH)₂D-mediated down-regulation (59, 60) of C/EBPa and PPARγ, the two master regulators of adipogenesis (63). Other mechanisms such as antagonisation of PPARγ activity and stabilisation of the VDR protein are also components of this complex regulation (69). Similar results, i.e. inhibited differentiation under 1,25(OH)₂D, have also been reported in brown adipocytes (64).

However, these data have been recently challenged in human adipocytes where 1,25(OH)₂D enhanced adipocyte differentiation and lipid accumulation (43). Interestingly, a similar activation of adipogenesis was found in primary mouse pre-adipocytes (albeit at a more advanced stage of differentiation compared with 3T3-L1 cells, suggesting that stage of differentiation is a key factor in the nature of the effect of 1,25(OH)₂D on adipogenesis). Similarly, 1,25(OH)₂D also increased adipogenesis in human adult stem cells derived from adipose tissue, as revealed by lipid accumulation and expression of adipogenic markers (65).

To summarise, the effects of 1,25(OH)₂D and VD on adipogenesis are not fully consistent: VD appears to act as a promoter of adipogenesis, but 1,25(OH)₂D has less clear effects. It is currently difficult to firmly conclude in favour of an anti- or pro-adipogenic effect, and further in vivo studies are required to clarify this point.

Regulation of gene expression linked to energy metabolism

VD and particularly 1,25(OH)₂D may also influence adipose tissue and systemic biology. Indeed, 1,25(OH)₂D directly up-regulated leptin expression and secretion,
independently of fat mass modifications\cite{66}. 1,25(OH)\textsubscript{2}D was found to promote glucose uptake by adipocytes\cite{67}, which could be related to the induction of GLUT4 protein expression and translocation observed in 3T3-L1 adipocytes\cite{68}. We showed that VD supplementation in mice led to an increase of fatty oxidation (especially in brown adipose tissue) that could be responsible for a high-fat diet-induced limitation of body weight gain in VD-supplemented mice\cite{69}. Note that similar weight gain limitations in response to VD supplementation have been reported in mice\cite{70} while VD-deficient old rats showed fat mass gain\cite{71}. Likewise, a global dietary vitamin restriction was associated with an increase of adiposity and a disruption of glucose homeostasis\cite{72} in mice.

Taken together, these data suggest that VD regulates energy expenditure, notably via its impact on adipose tissue biology.

Regulation of inflammation

Initial studies performed on human and mouse adipocytes (3T3-L1) found that 1,25(OH)\textsubscript{2}D up-regulates several inflammatory cytokines and down-regulates anti-inflammatory cytokines in both cell types\cite{73,74}. These results have since been challenged by several groups\cite{67,75-77} who consistently report anti-inflammatory effects of 1,25(OH)\textsubscript{2}D whatever the model studied, which fits better with the well-described anti-inflammatory effect of VD in many other cell types\cite{78}. Indeed, it was shown that 1,25(OH)\textsubscript{2}D significantly decreased the release of IL-8, monocyte chemotactatrant protein (MCP)-1 and IL-6 by human preadipocytes\cite{76} and MCP-1 by human adipocytes\cite{77}. These anti-inflammatory effects were associated with inhibition of the NF-κB signalling pathway\cite{78}. We also demonstrated the anti-inflammatory properties of 1,25(OH)\textsubscript{2}D in murine and human adipocytes\cite{67}. In these various models, 1,25(OH)\textsubscript{2}D was able to decrease the expression of inflammatory markers such as IL-6, IL-1β and MCP-1 in both basal and TNFα-stimulated conditions\cite{67}. Similarly, 1,25(OH)\textsubscript{2}D reduced the expression of IL-6, IL-8 and MCP-1 in human adipose tissue biopsies submitted to IL-1β stimulation in vitro\cite{79}. The molecular mechanisms have been investigated, and VDR and NF-κB signalling pathways and p38 mitogen-activated protein kinases were shown to be involved in 3T3-L1 adipocytes\cite{67}. Interestingly, Zoico et al. recently demonstrated that VD, similarly to 1,25(OH)\textsubscript{2}D, was able to blunt the lipopolysaccharide-mediated pro-inflammatory effect in human adipocytes\cite{67}. Using a microarray approach, we recently demonstrated that 1,25(OH)\textsubscript{2}D was able to down-regulate a large set of chemokines\cite{80} induced by inflammatory stimulus\cite{78} in human and murine adipocytes. This effect was accompanied by a reduction of macrophage migration mediated by an adipocyte-conditioned medium\cite{80}.

These anti-inflammatory properties of 1,25(OH)\textsubscript{2}D have also been established in several types of immune cells found in the adipose tissue, including lymphocytes and macrophages\cite{79}. Furthermore, 1,25(OH)\textsubscript{2}D reduced macrophage-induced inflammatory response in human adipocytes via inhibition of NF-κB and mitogen-activated protein kinase activation together with monocyte migration mediated by the adipocyte-conditioned medium\cite{82}. These data suggest that VD not only blunts adipocyte response to inflammatory stimulus, but also interferes with macrophage/adipocyte cross-talk, a key element of the propagation of metabolic inflammation in obesity\cite{83}.

The anti-inflammatory effect of VD in adipose tissue has also been observed in vivo. It was reported that dietary treatment with 1,25(OH)\textsubscript{2}D-reduced IL6 protein content in the epididymal adipose tissue of obese mice\cite{84}, whereas feeding with a VD-deficient high-fat diet was found to increase IL-6 expression in rat adipose tissue\cite{85}. In addition, we recently demonstrated that VD supplementation of high-fat diet reduced the expression of proinflammatory cytokines and chemokines and inhibited macrophage infiltration in the adipose tissue of obese mice\cite{69}. Similar effects of VD supplementation were found in an acute inflammation model (intraperitoneal injection of LPS) where no modification of body weight was measured\cite{85}, which strongly suggests that the decreased inflammatory status of adipose tissue observed in obese mice is not only a consequence of reduced fat mass\cite{69} but is also driven by an anti-inflammatory effect of VD per se.

To summarise, it has been demonstrated in vitro and in vivo that VD has a limiting effect on adipose tissue inflammation, acting on both inflammatory status in preadipocytes and adipocytes and on leukocyte infiltration.

Energy metabolism in transgenic mice models impacting vitamin D metabolism

Several transgenic mice models generated over the last decade have been used to gain insight into the role of VD metabolism in body weight management and adipose tissue metabolism. Studies using transgenic mouse models have shown that Vd\textsuperscript{−/−} and Cyp27b1\textsuperscript{−/−} mice (which are unable to synthesise 1,25(OH)\textsubscript{2}D) are resistant to diet-induced obesity\cite{86,87}. This phenotype was linked to the co-induction of fatty acid β-oxidation and uncoupling proteins in adipose tissue leading to increased energy expenditure in these mice. Conversely, overexpression of human VDR in mouse adipose tissue induced an obese phenotype characterised by increased weight and fat mass due to decreased energy expenditure, reduced fatty acid β-oxidation and lipolysis\cite{88}.

Taken together, these data strongly suggest that VDR or 1,25(OH)\textsubscript{2}D has an impact on overall energy metabolism by acting on adipose tissue biology, but with a number of caveats. First of all, the use of global knockout models makes it difficult to attribute the observed phenotype to a specific tissue. In addition, these mice were fed a rescue diet containing large amounts of calcium and lactose, and calcium is strongly suspected to regulate energy homeostasis and well known to reduce intestinal lipid absorption\cite{89}. Moreover, in wild-type mice, high-calcium rescue diet\cite{86} has been shown to reduce 1,25(OH)\textsubscript{2}D to extremely low levels similar to Cyp27b1\textsuperscript{−/−} mice\cite{90}, making it unlikely that the observed effect on body weight is attributable to 1,25(OH)\textsubscript{2}D.
In all these animal models (Vdr−/−, Cyp27b1−/− and human VDR overexpression), phenotype appears tightly linked to uncoupling protein-1 modulation[46–88]. However, we now know that unliganded VDR can down-regulate uncoupling protein-1[91], which means the VDR knockout could trigger an increase in uncoupling protein-1 leading to obesity resistance independently of plasma or adipose tissue levels of 1,25(OH)2D or other VD metabolites. In this case, the resistance to diet-induced obesity observed in Vdr−/− mice would be only VDR-dependent and not mediated by its ligand[87]. This would also be the case of human VDR overexpression where a down-regulation of uncoupling protein-1 is associated with weight gain[88].

Mechanistic explanations to these prospective observations are scarce. Indeed, the impact of VD on the regulation of energy metabolism in human subjects is still unclear[89]. Baseline 25(OH)D was positively correlated to diet-induced thermogenesis[90] which could at least partly explain why low 25(OH)D concentrations chronically modify energy balance. However, Boon et al. reported no effect of VD supplementation on energy expenditure and fat metabolism, but it should be noted that their supplementation regime was for 1 week only[91].

Intervention studies have been designed to study the causality between low plasma 25(OH)D levels and obesity. Except for Salehpour et al.[92], who reported that VD supplementation decreased body fat mass in healthy overweight and obese women, most randomised clinical trials have failed to demonstrate any benefit of VD supplementation in terms of weight loss[93–95]. These data were recently meta-analysed, and the lack of major effect of VD supplementation on weight loss was confirmed[96]. However, a well-designed randomised controlled trial combining a weight loss programme together with placebo or VD supplementation highlighted that VD supplementation was associated with a significantly higher reduction of BMI and waist circumference in subjects with 25(OH)D levels raised to 80 nm/l[97], suggesting that beneficial effects of the supplementation only kick in with elevated plasma 25(OH)D levels.

A recent study using Mendelian randomisation of several thousands of volunteers of different age, gender and geographical location demonstrated that an increase in BMI could cause a decrease in 25(OH)D status, whereas VD insufficiency would at most result in only very minor effects on obesity[98]. Note that the study only focused on genes related to 25(OH)D status (VDBP, DHCRTL, CYP2R1 and CYP24A1) and chosen on the basis of a genome-wide association study[99] that explained 1–4% of the variation in 25(OH)D concentrations, and so it cannot be ruled out that the use of polymorphisms present in other VD-related genes (such as VDR or CYP27B1) as instrumental variables of the Mendelian randomisation may lead to divergent results. Another large-scale study including Chinese women failed to show an association between obesity and genetic variants in genes in the pathway of VD metabolism[100], whereas the relationship between obesity and 1,25(OH)2D is less clear. Recent studies have reported an inverse relationship between 1,25(OH)2D and BMI and fat mass[101,102] while an older study found a direct relationship[103]. The origin of these inconsistent results is unclear but could stem from methodological bias in calcitriol measurement or else indicate that serum 1,25(OH)2D displays an inter-individual variability that is not adiposity-related. Also, no data are available on 1,25(OH)2D concentration in adipose tissue, which could be the critical effecter in relation to obesity.

Numerous cross-sectional studies have reported a correlation between VD deficiency and obesity. Indeed, serum 25(OH)D is consistently lower in obese than lean individuals[94]. A recent meta-analysis found that prevalence of VD deficiency was 35% higher in obese and 25% higher in overweight compared with lean subjects[95]. In addition, 25(OH)D plasma levels are inversely correlated to all the parameters of obesity, including BMI, fat mass and waist circumference[96,97], and increased dietary intake of VD, resulting in higher 25(OH)D plasma levels, is associated with a lower visceral adiposity[98].

Effects of vitamin D on obesity and associated disorders in human studies

The fact that adipose tissue is the main storage site for VD and/or its metabolites in the body has prompted the hypothesis that VD and/or its metabolites gets sequestered in the excess fat mass in obese persons[89]. However, the physiological mechanisms underlying this hypothesis have not been brought forward. Nevertheless, as pointed out in a recent study from Drincic et al.[100], it might just be that in individuals with a higher body mass, 25(OH)D is simply diluted in a higher volume, so they would require greater VD input than lean individuals to achieve a sufficient 25(OH)D status. Decreased plasma 25(OH)D levels could also result from a modification in VD metabolism occurring during obesity development. Indeed, modifications in the expression of genes encoding key enzymes of VD metabolism have been reported in the adipose tissue of obese people[38].
several other studies found associations, notably between VDR polymorphisms and adiposity\(^{(123)}\). The origin of these discrepancies has not been established but could stem from ethnic specificities, since it is well established that ethnicity is a significant determinant of plasma 25(OH)D\(^{(122)}\).

Taken together, these data suggest that VD may limit weight gain in human subjects even if it has no clear effect on weight reduction in obese or overweight people. However, clinical trials are needed to provide conclusive proof and to define the mechanisms governing this potential preventive effect of VD against obesity development. The question of the impact of VD supplementation and polymorphisms present in genes coding for key enzymes of VD metabolism remains unclear, and will require further investigations. Equally useful would be studies on the impact of VD supplementation on adipose tissue biology in well-designed randomised clinical trials that should follow several criteria, chiefly low baseline 25(OH)D, use of doses necessary to raise 25(OH)D concentrations up to 75–80 nm/l, and genotyping subjects.

**Conclusions**

Recent data from different research groups are converging to highlight the impacts of VD on adipose tissue/adipocyte biology. One of the best-documented effects is the ability of VD to limit the expression for inflammatory markers in adipose tissue and adipocytes. However, several key points urgently warrant further investigation, chiefly VD metabolism and its regulation in adipose tissue, which needs to be clarified, especially in the context of physiopathological disorders such as obesity. The last 5 years have seen some very interesting data in transgenic mice and rodents subjected to VD supplementation or restriction, but still without convergent findings. It is urgent to identify the origin of these discrepancies, where a key factor could be the quantification of VD metabolites in adipose tissue. Randomised clinical trials have been performed, but again the results remain contrasted, leaving persistent uncertainty over a beneficial role of VD supplementation on weight management. However, results from a recent intervention study suggest that a minimum level of plasma 25(OH)D has to be reached in order to elicit a beneficial effect from supplementation, since only subjects that became replete showed improvements in several parameters\(^{(116)}\). This observation is consistent with successful investigations in mice where plasma 25(OH)D levels were inflated. This same study also demonstrates that it is important to stratify the data according to 25(OH)D status in order to explore and interpret differential physiological responses at the end of the supplementation period, an approach that should be used in future clinical studies. Recent prospective studies have presented low plasma 25(OH)D levels as a predictor of body weight gain, suggesting that VD may limit the prevalence of obesity. If these observations are confirmed in dedicated well-designed clinical studies, it could pave the way to the use of VD in preventive nutrition to limit the development of obesity and associated disorders, notably by reducing the inflammatory status.

To conclude, even if preclinical studies have provided strong support for beneficial impacts of VD supplementation, well-designed clinical studies are urgently needed to demonstrate real valuable utility for limiting obesity in human subjects.

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**Conflict of Interest**

None.

**Authorship**

All authors participated in writing up this review.

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