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Vitamin D, adipose tissue and obesity

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Abstract

Epidemiological studies have shown a link between vitamin D deficiency and numerous pathologies such as cancers, immunity diseases, cardiovascular diseases, hypertension, type 2 diabetes and obesity.

Recent studies in vitro and in animal models demonstrated **an impact of** vitamin D on adipose tissue and adipocyte biology. Such observations are of particular interest and provide mechanistic explanations on the relationship between vitamin D deficiency and obesity.

Introduction

Vitamin D comes from two sources: exogenous but also endogenous, contrarily to other vitamins [1]. Endogenous synthesis of vitamin D is performed in the epidermis, which is able to produce this vitamin in large quantities after exposure to ultraviolet radiation B. It is synthesized from 7-dehydrocholesterol, a **precursor** of cholesterol, present in the cell membranes of the epidermis [2] (Figure 1). The energy supplied by ultraviolet B allows its transformation into pre-vitamin D₃, which is converted in vitamin D₃ under the effect of heat, before being released into the circulation. The synthesis of vitamin D is closely related to sun exposure. Classically it has been estimated that 80% to 90% of vitamin D in the body came from sun exposure (159). However, a recent article re-estimates that sun synthesis contributes only to 10-25% of vitamin D supply [3].

Vitamin D can also be provided through the diet. The vitamin D is present in two forms: the vitamin D₂ form (ergocalciferol), mainly produced by plants and fungi in particular and the vitamin D₃ form (cholecalciferol), synthesized in animals [4]. Only a limited number of foodstuffs contain vitamin D in significant amount. The main sources of vitamin D are fish

liver oils, some fatty fish (sardines, herring, mackerel), the egg yolk or the chicken liver [5].

Vitamin D is also found in small quantities in milk, orange juice, bread or cereals.

Vitamin D metabolism

Vitamin D is partially absorbed in the distal part of the small intestine, in emulsion with bile salts. Its intestinal absorption occurs not only by passive diffusion but involves, in part, two cholesterol carriers [6]. After absorption, vitamin D reaches the liver via the circulation where it is bound to the vitamin D Binding Protein (VDBP). Vitamins D₂ and D₃ have a substantially identical metabolism, which depends on the same enzymatic complex in humans. Whatever its origin (endogenous or exogenous), vitamin D is stored in adipocytes. Indeed, in rats, it has been established that fat is the main storage site for vitamin D, where half of it is stored as non-metabolized vitamin D and the other half as polar metabolites, vitamin D esters, and unidentified compounds [7]. In obese patients, vitamin D was measured in subcutaneous adipose tissue [8] and visceral adipose tissue [9] confirming that adipose tissue is also a vitamin D reservoir in humans.

In the liver, vitamin D is hydroxylated on carbon 25 to form 25(OH)-vitamin D₃ (25(OH)D). Several enzymes can accomplish this first hydroxylation of 25-hydroxyvitamin D₃ (25(OH)D) but CYP2R1 seems to be the key one [10]. After its first hydroxylation, 25(OH)D circulates in the blood, its half-life is relatively long (15 days) and the mean plasma concentration varies between 20 and 50 ng / ml (78-125 nmol / l) [11].

Vitamin D enters in the proximal renal tubule cells, either in its free form (unbound to DBP), or in association with the DBP, where it can be hydroxylated on the carbon 1 to form 1,25(OH)₂D [12]. 1 α -hydroxylase (CYP27B1) is highly expressed in the kidney and is

responsible for the conversion of 25(OH)D into 1,25(OH)₂D or calcitriol, which is considered as the main vitamin D active form. The activity of renal 1 α -hydroxylase is regulated by the parameters of bone and mineral metabolism. It is mainly stimulated by the parathyroid hormone (PTH). 1,25(OH)₂D is active in different organs. Its half-life is very short (about 4 hours) and its concentration is a thousand times less than the plasmatic vitamin 25(OH)D concentration.

The metabolism of vitamin D is self-regulated. Indeed, calcitriol induces the expression of 24-hydroxylase (CYP24A1) that converts 25(OH)D and 1,25(OH)₂D into inactive metabolites (i.e. 24,25(OH)₂D and 1,24,25(OH)D₃ vitamin D) which are further catabolized into inactive calcitroic acid [12]. Other enzymes of the cytochrome P450 family, such as CYP3A4, may also degrade calcitriol [10]

Furthermore, many cells express 1 α -hydroxylase, which can be locally controlled by signals independent of phosphocalcic metabolism, allowing extra-renal synthesis of 1,25(OH)₂D [13]. In this case, the 25(OH)D enters in these tissues and is hydroxylated into 1,25(OH)₂D to act locally, the excess being metabolized to inactive compounds.

Vitamin D signalization.

Even if few VDR-independent effects of 1,25(OH)₂D have been documented [14], this hormone mainly exerts its effects by binding to the nuclear vitamin D receptor (VDR), a member of the nuclear receptor superfamily [15]. It is the only nuclear protein that binds 1,25(OH)₂D with high affinity [16]. The expression of VDR has been demonstrated in almost all human tissues [13], 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 retinoic acid receptor (RXR) [17] and the RXR-VDR-1,25(OH)₂D complex binds to the DNA of sites called vitamin D response elements (VDRE), in the promoter region of genes whose expression is either activated or repressed [15]. More than 1000 genes are under the direct or indirect regulation of 1,25(OH)₂D, in various physiological process such as cell proliferation, differentiation, apoptosis and angiogenesis [18].

Vitamin D deficiency and insufficiency

Several factors can lead to vitamin D insufficiency or deficiency. The main one is the reduction of cutaneous synthesis, which may result from a lack of sun exposure (urban life, wearing protective clothing, photoprotection related to skin cancer prevention, sun allergy or photosensitivity) and also from the geographical position (beyond the 35th degree of north latitude, the capacity for synthesis is considered as null or almost null between November and February) [2]. The concentration of 7-dehydrocholesterol in the deeper layers of the skin also decreases with age; a 70 year old person produces 4 times less vitamin D than about 20 years old [19]. The skin pigment (melanin) is a natural sunscreen and increasing the melanin pigmentation can reduce the synthesis of vitamin D as effectively as a sunscreen with an index of protection to 15 [20]. Thus, the prevalence of vitamin D deficiency is higher in patients with dark skin [21]. The synthesis of vitamin D is also decreased by more than 90% by sunscreens which have an index of protection higher than or equal to 15. Certain medications such as steroids and some enzyme inducers activate the nuclear receptor Steroid and Xenobiotic Receptor (SXR) and in this way induce increased expression of CYP3A4, which increases the catabolism of 1,25(OH)₂D [1]). Finally, obesity can lead to vitamin D deficiency by reducing its bioavailability through dilution in adipose tissue [22].

Relationship between vitamin D and obesity

Numerous epidemiological studies have suggested a link between vitamin D deficiency and obesity development because obese people tend to have low plasma levels of 25(OH)D [23, 24]. The plasma levels of 25(OH)D levels are inversely correlated to all the parameters of obesity including: BMI, fat mass and waist circumference. Interestingly, increased dietary intake of vitamin D, resulting in higher 25(OH)D plasma levels, is linked to a lower visceral adiposity [25]. The relationship between obesity and the active form of vitamin D (1,25(OH)₂D) is less clear. Recent studies have reported an inverse relationship between 1,25(OH)₂D and BMI and fat mass while older studies show a direct relationship [26, 27]. The origin of this difference is not clear and could result of methodological bias in calcitriol measurement.

Classically the low plasma levels of 25(OH)D have been attributed to the expansion of adipose tissue that would sequester vitamin D, thereby reducing its availability in the circulation (218,219). However, a recent study mentioned that lower plasma 25(OH)D in obese population would actually result from the volumetric dilution of 25(OH)D (161). Such decrease of plasma level 25(OH)D could also result from a modification of vitamin D metabolism that occurs during obesity. Indeed, modifications of the expression of genes encoding key enzymes of vitamin D metabolism have been depicted in the adipose tissue of obese people [28].

In human, intervention studies have brought contrasted results. In a recent clinical trial, dietary supplementation with calcium and vitamin D for 16 weeks was associated with a reduction of visceral fat in overweight and obese adults [29]. However, other randomized

clinical trials failed to demonstrate any benefit of a vitamin D supplementation in terms of weight loss [30, 31].

This question remains thus highly controversial and will require well-designed RCT to clarify this point. At the opposite, results generated in vitro and in animal models are consistent with the hypothesis of an impact of vitamin D on adipose tissue biology.

Effects of vitamin D on the biology of adipose tissue

Adipogenesis

Many studies have examined the role of $1,25(\text{OH})_2\text{D}$ in proliferation, differentiation and metabolism of 3T3-L1 pre-adipocytes [32, 33]. It has been shown that low concentrations of $1,25(\text{OH})_2\text{D}$ could inhibit adipogenesis and reduce the accumulation of triglycerides. In addition, treatment of preadipocytes with other metabolites of vitamin D, such as $24,25(\text{OH})_2\text{D}$ can also inhibit the differentiation of pre-adipocytes, but only by using supra-physiological concentrations. This would be related to their low affinity for the vitamin D receptor (VDR). One of the early effects of $1,25(\text{OH})_2\text{D}$ on 3T3-L1 cells is increasing mRNA expression of VDR [32]. This suggests that the role of vitamin D in adipogenesis is VDR-dependent. The molecular mechanisms involve a dose-dependent inhibition of a number of genes involved in early and late stages of adipocyte differentiation including $\text{CEBP}\alpha$, $\text{PPAR}\gamma$, lipoprotein lipase (LPL) and adipocyte protein 2/adipocyte specific fatty acid-binding protein (aP2/FABP4), but also sterol-regulatory element-binding protein (SREBP) -1 and fatty acid synthase (FAS) [32]. In addition, the authors observed that the removal of $1,25(\text{OH})_2\text{D}$ after three days of treatment allowed the differentiation process to be restarted. This crucial

observation suggests that the main action of vitamin D on adipogenesis is the removal of a reversible key molecular event that occurs early in the differentiation process of preadipocyte. Finally, this study also suggests that 1,25(OH)₂D inhibits adipogenesis by antagonizing transactivation of PPAR γ and stabilizing the VDR protein.

However these data were not confirmed in human adipocytes where 1,25(OH)₂ enhanced adipocyte differentiation [34]. Interestingly, similar activation of adipogenesis was found in primary mouse preadipocytes (albeit at a more advanced stage of differentiation compared to 3T3-L1 cells), suggesting that the stage of differentiation is particularly important regarding the nature of the effect of 1,25(OH)₂D on adipogenesis.

Metabolism

It is now well established that the vitamin D receptor (VDR) has many activities including the regulation of the biology and metabolism of adipocytes. An initial study showed that 1,25(OH)₂D induced a significant increase in the activity of lipoprotein lipase (LPL) and the amount of its mRNA in 3T3-L1 adipocytes [35]. At the same time, the fatty acid synthase (FAS), which catalyzes the lipogenesis is down-regulated by 1,25(OH)₂D in 3T3-L1 adipocytes [36]. In vivo studies were undertaken using transgenic mouse models and it has been shown that mice VDR^{-/-} or CYP27B1^{-/-} (which are unable to synthesize 1,25(OH)₂D) are resistant to diet-induced obesity [37, 38]. Conversely, overexpression of human VDR in mice adipose tissue induces an obese phenotype characterized by increased weight and fat mass, due to a decrease in energy expenditure, reduced fatty acid β -oxidation and lipolysis [39]. These data strongly suggest that VDR and 1,25(OH)₂D have an impact on the overall metabolism by producing particular effects on adipose tissue. However, the specific effects that could be induced by vitamin D supplementation in this context are still unknown.

In humans, even if vitamin D intake is considered as a predictor of body mass index [40], the impact of vitamin D on regulation of energy metabolism is **not clear**. Baseline 25(OH)D was positively correlated to diet-induced thermogenesis [41]. However, Boon et al. reported no effect of vitamin D supplementation on energy expenditure and fat metabolism, but it is noteworthy that supplementation was conducted for one week only [26].

Inflammation

It is well known that obesity is associated with a low grade inflammatory status, partly caused by an increased production of proinflammatory cytokines by adipose tissue [42]. Several studies conducted on murine 3T3-L1 adipocytes and in human adipocytes have demonstrated that 1,25(OH)₂D increased the expression of inflammatory cytokines and, conversely, inhibited the expression of anti-inflammatory cytokines in both cell types [43, 44]. These results seemed paradoxical in relation to the anti-inflammatory effect of vitamin D well described in many other cell types [45]. Further studies have been undertaken by several groups, which led in 2012 to the publication of four papers relating to the anti-inflammatory effect of vitamin D on adipocytes or preadipocytes (Figure 2). These very consistent results all showed an anti-inflammatory effect of 1,25(OH)₂D whatever the model studied. Indeed, it was shown that 1,25(OH)₂D significantly decreased the release of IL-8, MCP-1 and IL-6 by human preadipocytes [46] and MCP-1 in human adipocytes [47]. These anti-inflammatory effects were associated with inhibition of the NF-κB signaling pathway [48]. Similarly, an anti-inflammatory role of 1,25 (OH)₂D has been demonstrated in murine and human adipocytes. 1,25(OH)₂D was able to decrease the expression of inflammatory markers such as IL-6, IL-1 beta and MCP-1. This effect was accompanied by an improvement in glucose uptake by adipocytes. The molecular mechanisms have been investigated and the involvement

of the VDR and NF- κ B signaling pathways and p38 MAP kinases was demonstrated [49]. In addition, these anti-inflammatory properties have also been established in several types of immune cells present in the adipose tissue, such as lymphocytes and macrophages [45]. These results suggest that vitamin D may have a role limited to obesity-associated adipose tissue inflammation, acting both on the inflammatory status of preadipocytes, adipocytes as well as leukocyte infiltration.

Personal opinion

Data recently generated by different research group highlight the impact of vitamin D on adipose tissue / adipocyte biology. However, clear confirmation in animal models as well as mechanistic explanations is urgently needed. The effect of vitamin D supplementation alone (i.e. without calcium supplementation) in diet induced obesity mice model has not been investigated so far in terms of weight management and inflammatory status. Several studies have been conducted in transgenic and knockout mice, which provide results in apparent contradiction with epidemiological studies. Some randomized clinical trials have been performed but results remain contrasted, leaving the beneficial role of vitamin D supplementation uncertain. Thus in a near future, we will strongly need well-designed supplementation experiments.

Several key points will require further investigations. It is notably the case of the vitamin D metabolism in adipose tissue / adipocytes, which needs to be clarified. Especially the impact of vitamin D on its own metabolism as well as the effect of physiopathological disorders such as obesity will require studies. These specific points are part of the knowledge urgently required to be more efficient in the design of relevant supplementation studies.

Highlights

25(OH)D level in plasma are inversely correlated to adiposity and BMI.

Adipose tissue is a physiological storage site for vitamin D.

Vitamin D and metabolites are active on adipocytes and adipose tissue biology.

1,25(OH)₂D generates anti-inflammatory effect and stimulates glucose uptake in adipocytes.

1,25(OH)₂D modulates adipogenesis.

VDR **negatively regulates** of energy homeostasis.

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Figures legends

Figure 1: Vitamin D synthesis, activation and catabolism.

The vitamin D metabolism. A simplified scheme showing the synthesis of cholecalciferol (vitamin D₃) from 7-dehydrocholesterol upon sunlight exposure and the subsequent two step activation. The first step in the liver which results in the formation of 25-hydroxyvitamin D₃ and the second step in the kidney via CYP27B1 leading to the active hormone 1,25-dihydroxyvitamin D₃.

Figure 2: Vitamin D decreases inflammatory process in adipocytes and preadipocytes.

Molecular mechanisms involved in the anti-inflammatory effects of 1,25-dihydroxyvitamin D₃.