Horizons in Nutritional Science

Vitamin D signalling in adipose tissue

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Abstract

Vitamin D deficiency and the rapid increase in the prevalence of obesity are both considered important public health issues. The classical role of vitamin D is in Ca homoeostasis and bone metabolism. Growing evidence suggests that the vitamin D system has a range of physiological functions, with vitamin D deficiency contributing to the pathogenesis of several major diseases, including obesity and the metabolic syndrome. Clinical studies have shown that obese individuals tend to have a low vitamin D status, which may link to the dysregulation of white adipose tissue. Recent studies suggest that adipose tissue may be a direct target of vitamin D. The expression of both the vitamin D receptor and 25-hydroxyvitamin D 1α,25-dihydroxylase (CYP27B1) genes has been shown in murine and human adipocytes. There is evidence that vitamin D affects body fat mass by inhibiting adipogenic transcription factors and lipid accumulation during adipocyte differentiation. Some recent studies demonstrate that vitamin D metabolites also influence adipokine production and the inflammatory response in adipose tissue. Therefore, vitamin D deficiency may compromise the normal metabolic functioning of adipose tissue. Given the importance of the tissue in energy balance, lipid metabolism and inflammation in obesity, understanding the mechanisms of vitamin D action in adipocytes may have a significant impact on the maintenance of metabolic health. In the present review, we focus on the signalling role of vitamin D in adipocytes, particularly the potential mechanisms through which vitamin D may influence adipose tissue development and function.

Key words: Vitamin D; Adipose tissue; Adipocytes; Inflammation; Obesity

The vitamin D endocrine system has been linked historically to the aetiology of rickets(1). Growing evidence suggests that in addition to maintaining Ca homoeostasis and skeletal health(2,3), vitamin D has pleiotropic actions that can affect multiple organs and metabolic processes, including in the cardiovascular, renal and immune systems(4–7). It has been argued that vitamin D deficiency as a global health issue may contribute to the pathogenesis of a number of disorders, including obesity, the metabolic syndrome and type 2 diabetes(8–13). Clinical and epidemiological studies show that obese individuals tend to have low vitamin D status(12–17). Although vitamin D bioavailability could be reduced in obesity due to increased sequestration by white adipose tissue(13,18), the mechanisms underlying the inverse relationship between adiposity and vitamin D deficiency are largely unknown. Interestingly, recent studies suggest that (white) adipose tissue could be a direct target of vitamin D, and that the hormone may modulate adipose tissue formation and function(19–23). Given the multiplicity of functions of white adipose tissue, and the link between dysfunction of the tissue and the pathogenesis of obesity and its co-morbidities, clarifying the role of vitamin D in adipose tissue may lead to public health benefits.

In the present article, we discuss recent advances in our understanding of the interactions between adipose tissue and vitamin D; we also raise questions on vitamin D signalling in adipose tissue, especially the molecular mechanisms underlying the mode of action of the hormone.

The vitamin D system

The two main forms of vitamin D are vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol)(24,25); however, vitamin D₃...
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is the only form that is found naturally in human subjects and other animals. Vitamin D₃ is synthesised in the skin from 7-dehydrocholesterol through exposure to UVB irradiation(25). The resulting pre-vitamin D (precholecalciferol) is converted to vitamin D₃ (cholecalciferol) via thermal isomerisation. 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. The main dietary sources of vitamin D include oily fish, egg yolks and fortified milk. Vitamin D₃, whether derived from sunlight or the diet, enters the circulation bound to vitamin D-binding protein and is transported to the liver. Vitamin D₃ is hydroxylated in the liver to form 25-hydroxycholecalciferol (25(OH)D₃), the major circulating vitamin D metabolite. 25(OH)D₃ is then further hydroxylated by a 1α-hydroxylase enzyme (gene: CYP27B1), and this occurs primarily in the kidney to produce 1α,25-dihydroxycholecalciferol (1,25(OH)₂D₃), the biologically active form of vitamin D. In vivo studies have shown that the catabolism of vitamin D and its metabolites occurs mostly in the liver through a variety of cytochrome P450 enzymes that produce a number of catabolites(26,27). The 24-hydroxylase (gene: CYP24), a mitochondrial cytochrome P450-containing enzyme, catalyses several steps in 1,25(OH)₂D₃ degradation through 24-hydroxylation and the formation of calcitriolic acid(28).

**Vitamin D receptor**

The action of 1,25(OH)₂D₃ is mediated through the vitamin D receptor (VDR), a member of the nuclear receptor superfamily, which regulates the transcription of many target genes(29,30). VDR binds to 1,25(OH)₂D₃ with high affinity and specificity, which then heterodimerises with a retinoid X receptor(31). Once the heterodimer binds with vitamin D response elements in target genes, a genomic response is generated(32,33). In addition, there is also a plasma membrane VDR which mediates the acute, rapid actions of 1,25(OH)₂D₃(34). VDR has been identified in most human tissues, including in osteoblasts, skin keratinocytes, macrophages, smooth muscle, pancreatic β-cells and epithelial cells(35,36). The ubiquitous expression of VDR may underlie the diverse effects of vitamin D and provide a mechanistic basis for the link between vitamin D deficiency and a number of disorders, including certain types of cancer, inflammatory bowel disease, CVD, diabetes (type 1 and type 2) and the metabolic syndrome(11,36–39).

**Vitamin D deficiency and obesity**

Clinically, vitamin D status is normally assessed by measurement of the serum level of 25(OH)D₃, the major form of vitamin D in the circulation, with a half life of between 15 and 50 d(40–42). Vitamin D deficiency has been defined as a serum 25(OH)D₃ level of <20 ng/ml or <50 nmol/l(43,44). Studies on vitamin D status have suggested that there is a link between vitamin D deficiency and obesity as obese individuals tend to have low serum levels of 25(OH)D₃(17,45,46). Serum 25(OH)D₃ levels are found to be inversely correlated with measures of obesity, including BMI, fat mass and waist circumference(47–51). Furthermore, a negative association between 25(OH)D₃ and visceral fat has been demonstrated in African-Americans with diabetes(52). It is suggested that lower levels of circulating 25(OH)D₃ in obese individuals could be due to greater sequestration by adipose tissue, reducing its availability in the circulation(15,18). There is evidence that increased dietary vitamin D intake and elevated serum 25(OH)D₃ are related to lower visceral adiposity and omental adipocyte size in women undergoing gynaecological surgery(53). In a recent double-blind, placebo-controlled trial, dietary supplementation with Ca and vitamin D for 16 weeks was associated with a beneficial reduction of visceral fat in overweight and obese adults(54).

The relationship between obesity and the active form of vitamin D, 1,25(OH)₂D₃ (which has a short half life of approximately 15 h residence in the circulation(41)), is less clear, and this is probably due to the dynamic nature of the production and regulation of the active hormone. However, in healthy adults, low serum 1,25(OH)₂D₃ levels are associated with higher BMI and body fat mass(14,55,56). Similarly, data from a study of 2000 obese subjects have shown a negative correlation between BMI and serum 1,25(OH)₂D₃. Taken together, the present evidence strongly suggests that the vitamin D system is altered in obese subjects and this may have implications both for the development of obesity itself and of its co-morbidities.

**Vitamin D system in adipose tissue**

Recent studies suggest that the key components of the vitamin D system are evident in adipose tissue, and vitamin D could be involved in the function of the tissue(21,57,58). Expression of the CYP27B1 gene, which encodes the enzyme converting 25(OH)D₃ to 1,25(OH)₂D₃, has been reported in mouse 3T3-L1 preadipocytes and in adipose tissue of Wistar rats(31). Recent studies from our group and others have shown that CYP27B1 is expressed by Simpson–Golabii–Beymel Syndrome human adipocytes and preadipocytes(59,60) and by human mammary adipocytes(19). The CYP24 gene, which encodes the enzyme catalysing 1,25(OH)₂D₃, is also found to be expressed by murine 3T3-L1 adipocytes and by human adipocytes and preadipocytes(19,21,59,60). Thus, adipocytes could be involved in the local synthesis as well as degradation of biologically active vitamin D.

Although expression of the VDR gene has been reported in mouse white and brown fat and in 3T3-L1 adipocytes(25,61), little is known on whether human adipose tissue expresses VDR. We have, however, recently observed that the VDR gene is expressed by human adipose tissue (subcutaneous and visceral) (unpublished results) as well as by human fat cells in culture (preadipocytes and differentiated adipocytes)(59,60). Importantly, the bioactivation of 25(OH)D₃ to 1,25(OH)₂D₃ has been demonstrated very recently in human mammary adipocytes, together with the release of 1,25(OH)₂D₃(19). The basal and substrate-induced 1,25(OH)₂D₃ secretion by mature adipocytes is reported to be higher than with human mammary epithelial cells; these cells are known to be highly

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efficient at bioactivating 25(OH)D₃. This finding suggests that mature adipocytes are capable of taking up 25(OH)D₃, converting it to 1,25(OH)₂D₃, and then releasing the biologically active hormone to the adjacent microenvironment – and possibly to the circulating pool (nevertheless, the kidney is the major source of circulating 1,25(OH)₂D₃).

Macrophages are known to play a role in vitamin D metabolism, with the ability to convert circulating 25(OH)D₃ to 1,25(OH)₂D₃ (62). Adipose tissue expansion in obesity is associated with an increase in macrophage accumulation in the tissue (65,64), which may facilitate the local hydroxylation of 25(OH)D₃. However, the specific characteristics of adipose tissue macrophages and their potential contribution to the local production of 1,25(OH)₂D₃ need to be clarified.

Data on the actual 1,25(OH)₂D₃ content of human adipose tissue are very limited. In a small study of seventeen morbidly obese subjects undergoing gastric bypass surgery, the 1,25(OH)₂D₃ concentrations measured by liquid chromatography–MS (LC/MS) were much higher (>10-fold) in abdominal subcutaneous fat than in serum (18). Whether there is a rise in 1,25(OH)₂D₃ levels in adipose tissue, either by increased uptake or through local conversion in the obese state, is not known. Collectively, these findings suggest that human adipose tissue could well be a target for vitamin D, through endocrine as well as autocrine/paracrine actions of the hormone (Table 1).

Role of vitamin D in adipogenesis

Vitamin D and its receptor VDR have been implicated in the modulation of preadipocyte differentiation into adipocytes (adipogenesis) (65). The differentiation of 3T3-L1 (and other) preadipocytes is a highly controlled process through sequential induction of transcription factors that regulate the expression of adipocyte-specific markers. During adipogenesis, a series of cellular events begins with the rapid expression of C/EBPb, which serves as a late marker of adipogenesis (65). The differentiation of 3T3-L1 cells and its expression levels are maintained by 1,25(OH)₂D₃ during the course of adipocyte differentiation (65). In the presence of 1,25(OH)₂D₃, VDR inhibits adipogenesis by reducing C/EBPb mRNA and C/EBPb nuclear protein levels at a critical stage of differentiation (65). In addition, 1,25(OH)₂D₃ induces the up-regulation of C/EBPb corepressor, eight-twenty-one (ET0), which would further restrain the activity of remaining C/EBPb (65). A recent study has shown a positive association between VDR polymorphisms and the parameters of adiposity (58). VDR gene variants with polymorphisms on the 3’ UTR site, which affect the expression of VDR, are postulated to suppress the anti-adipogenic effect of vitamin D (58). Interestingly, a role for unliganded VDR in adipogenesis has been proposed, as VDR overexpression suppresses 3T3-L1 preadipocyte differentiation.

Table 1. Vitamin D-related gene expression identified in adipose tissue and adipocytes

<table>
<thead>
<tr>
<th>Vitamin D-related gene</th>
<th>Adipose tissue</th>
<th>Adipocyte</th>
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<tbody>
<tr>
<td><strong>VDR</strong></td>
<td>Rat adipose tissue (23)</td>
<td>Mouse 3T3-L1 (22,23,65,71)</td>
</tr>
<tr>
<td></td>
<td>Mouse adipose tissue (57)</td>
<td>Human mammary adipocytes (19)</td>
</tr>
<tr>
<td><strong>CYP27B1</strong></td>
<td>Rat adipose tissue (21)</td>
<td>Human SGBS adipocytes (and preadipocytes) (60)</td>
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<tr>
<td></td>
<td></td>
<td>Mouse 3T3-L1 (21)</td>
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<tr>
<td><strong>CYP24</strong></td>
<td>–</td>
<td>Human mammary adipocytes (19)</td>
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<tr>
<td></td>
<td></td>
<td>Human SGBS adipocytes (and preadipocytes) (60)</td>
</tr>
<tr>
<td><strong>CYP2R1</strong></td>
<td>–</td>
<td>Human SGBS adipocytes (and preadipocytes) (60)</td>
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VDR, vitamin D receptor; SGBS, Simpson–Golabi–Beymel syndrome.
in the absence of 1,25(OH)2D3. In contrast, the data from another study suggest that the unliganded VDR is required for lipid accumulation, as VDR knockdown with siRNA delays and prevents this process. However, in vitro studies on VDR function suggest that VDR could promote adipogenesis. Mice with a global VDR knockout had little fat mass and higher rates of β-oxidation in adipose tissue in comparison with wild-type controls. Thus, additional studies, including adipose tissue-specific knockout models, are required to clarify the function of VDR in adipogenesis.

Vitamin D and lipid metabolism

There is some evidence that vitamin D could be involved in lipid mobilisation and utilisation in adipose tissue. An early study observed that 1,25(OH)2D3 induces a significant increase in lipoprotein lipase activity and of its mRNA level in 3T3-L1 adipocytes. Concurrently, fatty acid synthase, which catalyses adipocyte lipogenesis, is down-regulated by 1,25(OH)2D3 in 3T3-L1 cells. However, in vitro functional studies of VDR suggest that the receptor could inhibit lipid mobilisation and utilisation. VDR-null mice were reported to be resistant to high-fat diet-induced obesity, probably due to increases in fatty acid β-oxidation in white adipose tissue and the expression of uncoupling proteins in brown fat and of overall energy expenditure. On the other hand, targeted expression of VDR in adipocytes induces obesity in mice without changes in food intake, which is mainly caused by a marked decrease in energy expenditure together with reduced lipolysis and β-oxidation in adipose tissue. In addition, the expression of genes involved in lipid metabolism, including hormone-sensitive lipase, adipose TAG lipase and uncoupling proteins 1, 2 and 3, is suppressed in VDR transgenic mice. Data on the effects of vitamin D in lipid metabolism in human subjects are scarce. A study of a small number of non-obese healthy subjects has shown that vitamin D supplementation (2000 IU cholecalciferol/d) together with a low dietary Ca intake for 7 d, had no effect on energy expenditure. However, a recent in vitro study has reported that vitamin D supplementation reduced IL-6 protein content in adipose tissue of mice fed a high-fat diet, and 1,25(OH)2D3 (100 nm) inhibited LPS-induced IL-6 production by 3T3-L1 adipocytes. More recently, 1,25(OH)2D3 (100 nm) has been shown to inhibit the release of MCP-1 and adiponectin by human adipocytes. The discrepancy between results might be due to the different doses used in these studies. Therefore, further work is needed to elucidate whether 1,25(OH)2D3 has a role in modulating the production of adipokines involved in inflammation.

Vitamin D and adipokine production

In addition to fuel storage, adipose tissue as an endocrine organ secretes a variety of bioactive proteins, and importantly a number of these adipokines, including adiponectin, TNF-α, IL-6 and monocyte chemoattractant protein-1 (MCP-1), are directly involved in inflammation. There are as yet few studies that have examined the possible role of vitamin D in the modulation of adipokine production. It has been shown that mice lacking the VDR or CYP27B1 genes have reduced levels of serum leptin. In a Middle-Eastern population of non-obese young subjects, serum 25(OH)D3 was found to be positively correlated with adiponectin levels, though inversely associated with several metabolic risk factors, suggesting a possible link between vitamin D status and circulating adiponectin concentrations.

There is some evidence that vitamin D3 may directly regulate adipokine expression and secretion by adipocytes. An in vitro study has shown that treatment with 1,25(OH)2D3 (10 nm) up-regulated the expression of the macrophage inhibitory factor (MIF), IL-6 and MCP-1 genes in 3T3-L1 adipocytes, and increased MIF mRNA levels in human adipocytes. However, a recent in vitro study has reported that vitamin D supplementation reduced IL-6 protein content in adipose tissue of mice fed a high-fat diet, and 1,25(OH)2D3 (100 nm) inhibited LPS-induced IL-6 production by 3T3-L1 adipocytes. More recently, 1,25(OH)2D3 (100 nm) has been shown to inhibit the release of MCP-1 and adiponectin by human adipocytes. The discrepancy between results might be due to the different doses used in these studies. Therefore, further work is needed to elucidate whether 1,25(OH)2D3 has a role in modulating the production of adipokines involved in inflammation.

Vitamin D and inflammation in adipose tissue

The potential role of vitamin D in modulating inflammation in obesity and other chronic diseases has received increasing attention. Evidence has accumulated that 1,25(OH)2D3 has potent immunoregulatory effects, such as inhibiting the production of IL-6, IL-8 and interferon-γ by peripheral blood mononuclear cells from psoriatic patients. It has also been shown that 1,25(OH)2D3 down-regulates the gene expression of toll-like receptor (TLR) 2 and TLR-4 in human monocytes. 1,25(OH)2D3 also suppresses peripheral blood mononuclear cells' proliferation and induces apoptosis in peripheral blood mononuclear cells of healthy subjects and inflammatory bowel disease patients. Both 1,25(OH)2D3 and 25(OH)D3 have been shown to reduce lipopolysaccharide-induced TNF-α and IL-6 production, probably by inhibiting p38 MAPK activation in human monocytes/macrophages. Conversely, 1,25(OH)2D3-deficient T-cells isolated from CYP27B1 knockout mice are predisposed to overexpress IL-1α, while VDR-null mice display a failure of T-cell homing to the gut with low levels of IL-10 in inflammatory bowel disease. Furthermore, in peripheral blood mononuclear cells from type-2 diabetic patients having a proinflammatory profile, 1,25(OH)2D3 is reported to act in an anti-inflammatory manner to decrease the expression of TNF-α, IL-1, IL-6 and IL-8. In vivo, aged mice treated with vitamin D3 showed a significant improvement in visual function by reducing retinal inflammation and amyloid-β accumulation.

With adipocyte hypertrophy in obesity, there is a marked increase in the synthesis and release of proinflammatory mediators (e.g. TNF-α, IL-6, IL-8 and MCP-1), and this
contributes to the raised circulating levels as well as to the tissue inflammation\(^\text{88,89}\). Adipose tissue inflammation, characterised by increased infiltration of macrophages and other immune cells, is a central pathological process in adipose tissue dysfunction\(^\text{90,91}\). Work from our group and others has demonstrated that macrophage-conditioned medium potently stimulates the release of proinflammatory factors (e.g. MCP-1, IL-8, chemokine (C–C motif) ligand 5 (CCL-5) and IL-6) and a number of proteins involved in extra-cellular matrix remodelling from human preadipocytes and adipocytes; these factors may induce inflammation, fibrosis and insulin resistance in adipose tissue\(^\text{59,92–95}\). The immunoregulatory effects of 1,25(OH)\(_2\)D\(_3\) suggest that the hormone may also modulate the inflammatory response in adipose tissue. Very recently, we have shown that treatment with 1,25(OH)\(_2\)D\(_3\) (10 and 100 nM) led to a reduction in the protein release of MCP-1 and IL-6 by human preadipocytes, as well as preadipocyte-induced macrophage migration\(^\text{96}\). Concurrently, an inhibitory effect of 1,25(OH)\(_2\)D\(_3\) on TNF-\(\alpha\)-stimulated MCP-1 release by human adipocytes has been reported\(^\text{79}\).

Activation of the NF-\(\kappa\)B signalling pathway is essential in the signal transduction of proinflammatory cytokines in many cell types, including adipocytes\(^\text{95,97,98}\). NF-\(\kappa\)B activation involves the degradation of I\(\kappa\)B\(\alpha\) protein and translocation of p65 into the nucleus\(^\text{99}\). Our recent work has shown that 1,25(OH)\(_2\)D\(_3\) can increase I\(\kappa\)B\(\alpha\) protein abundance in human preadipocytes\(^\text{96}\). Blocking of NF-\(\kappa\)B activation by 1,25(OH)\(_2\)D\(_3\) has also been reported in mesangial cells, as 1,25(OH)\(_2\)D\(_3\) can stabilise I\(\kappa\)B\(\alpha\), leading to an inhibition of p65 NF-\(\kappa\)B nuclear translocation\(^\text{100}\). Very recently, we have observed that 1,25(OH)\(_2\)D\(_3\) is able to reverse macrophage-elevated inhibition of I\(\kappa\)B\(\alpha\) and up-regulation of p65 NF-\(\kappa\)B in differentiated human adipocytes (unpublished results). Overall, 1,25(OH)\(_2\)D\(_3\) appears to be anti-inflammatory and it may ameliorate macrophage-induced inflammation in adipose tissue (Fig. 1).

**Vitamin D and insulin resistance**

Several clinical studies have associated low vitamin D status with the development of insulin resistance in adults\(^\text{8,76,101}\) and children\(^\text{102,103}\). Higher basal levels of 25(OH)D\(_3\) have been found to predict better \(\beta\)-cell function and lower glycaemia in subjects at risk for type 2 diabetes\(^\text{104}\). In rats, vitamin D deficiency impairs insulin release from the pancreas and...
reduces glucose tolerance, which is partially reversed following treatment with 1,25(OH)₂D₃. A recent clinical trial has shown that cholecalciferol (2000 IU daily) supplementation for 16 weeks improved β-cell function in adults at high risk of diabetes. In type 2 diabetic patients with vitamin D deficiency, daily intake of a vitamin D-fortified yogurt drink increased serum 25(OH)D levels and improved glycaemic status. Therefore, vitamin D may have an effect on insulin secretion from pancreatic β-cells and further work in this area is warranted.

A potentially beneficial effect of vitamin D on insulin sensitivity has been proposed, as 1,25(OH)₂D₃ treatment increased insulin receptor mRNA levels and insulin-stimulated glucose transport in U-937 promonocytic cells, possibly via the up-regulation of phosphatidylinositol 3-kinase activity. Adipose tissue, in addition to skeletal muscle and liver, is a key organ exhibiting insulin resistance in obesity. Although adipose tissue only accounts for approximately 10% of insulin-stimulated whole-body glucose uptake, the reduction in insulin sensitivity of adipocytes increases NEFA release into the circulation, which may induce hepatic and muscle insulin resistance. In streptozotocin-induced diabetic rats, 1,25(OH)₂D₃ treatment has been reported to normalise the number of insulin receptors and improve the insulin response to glucose transport in epididymal adipocytes. However, whether vitamin D metabolites have beneficial effects on glucose transport and insulin action in human adipose tissue remains to be investigated.

Conclusions

In conclusion, the vitamin D system has multiple physiological functions beyond its classical role in Ca homoeostasis and bone metabolism. Data from clinical studies have indicated that vitamin D deficiency is associated with several diseases, including obesity and type 2 diabetes. Emerging evidence suggests that adipose tissue could be a target for vitamin D actions, as the CYP27B1 and VDR genes are expressed by adipocytes of both rodents and human subjects. Recent in vitro studies suggest that 1,25(OH)₂D₃ may inhibit adipogenesis by suppressing the expression of the key adipogenic transcription factors and reducing lipid accumulation in adipocytes. Moreover, VDR overexpression in 3T3-L1 cells inhibits preadipocyte differentiation, and VDR polymorphisms are associated with increased adiposity in human subjects. However, functional studies of VDR in vivo have produced opposite results, as VDR-null mice exhibit a lean phenotype with reduced fat mass. Consistent with its immunomodulatory effects in other cell types, vitamin D appears to be anti-inflammatory in adipose tissue. This is particularly demonstrated by the inhibition of the expression and release of MCP-1 from human adipocytes by 1,25(OH)₂D₃. Therefore, it is probable that vitamin D has a regulatory role in adipose tissue function in health and disease. Further experimental and translational studies are needed to unravel the signalling role of vitamin D in adipose tissue, particularly its putative link to adipocyte dysfunction in obesity.

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