British Journal of Nutrition (2012), **108**, 1915–1923
doi:10.1017/S0007114512003285

British Journal of Nutrition

Horizons in Nutritional Science

Vitamin D signalling in adipose tissue

Cherlyn Ding[1], Dan Gao[1], John Wilding[1], Paul Trayhurn[1,2] and Chen Bing[1]*

[1]*Obesity Biology Research Group, Department of Obesity and Endocrinology, Institute of Ageing and Chronic Disease, University of Liverpool, Duncan Building, Liverpool L69 3GA, UK*
[2]*Clore Laboratory, University of Buckingham, Hunter Street, Buckingham MK18 1EG, UK*

(Submitted 3 April 2012 – Final revision received 12 June 2012 – Accepted 27 June 2012 – First published online 9 October 2012)

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-hydroxylase (*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[8–11]. 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 D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol)[24,25]; however, vitamin D_3

Abbreviations: $1,25(OH)_2D_3$, 1α,25-dihydroxycholecalciferol; $25(OH)D_3$, 25-hydroxycholecalciferol; C/EBP, CCAAT/enhancer-binding protein; MCP-1, monocyte chemoattractant protein-1; VDR, vitamin D receptor.

* **Corresponding author:** Dr C. Bing, fax +44 151 7065802, email bing@liverpool.ac.uk

is the only form that is found naturally in human subjects and other animals. Vitamin D_3 is synthesised in the skin from 7-dehydrocholesterol through exposure to UVB irradiation[25]. The resulting pre-vitamin D (precholecalciferol) is converted to vitamin D_3 (cholecalciferol) via thermal isomerisation. Although the main source of vitamin D_3 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 D_3, whether derived from sunlight or the diet, enters the circulation bound to vitamin D-binding protein and is transported to the liver. Vitamin D_3 is hydroxylated in the liver to form 25-hydroxycholecalciferol ($25(OH)D_3$), the major circulating vitamin D metabolite. $25(OH)D_3$ is then further hydroxylated by a 1α-hydroxylase enzyme (gene: *CYP27B1*), and this occurs primarily in the kidney to produce 1α,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$), 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 $1,25(OH)_2D_3$ degradation through 24-hydroxylation and the formation of calcitrioic acid[28].

Vitamin D receptor

The action of $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$ [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 $25(OH)D_3$, 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 $25(OH)D_3$ 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 $25(OH)D_3$[17,45,46]. Serum $25(OH)D_3$ 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 $25(OH)D_3$ and visceral fat has been demonstrated in African-Americans with diabetes[52]. It is suggested that lower levels of circulating $25(OH)D_3$ in obese individuals could be due to greater sequestration by adipose tissue, reducing its availability in the circulation[13,18]. There is evidence that increased dietary vitamin D intake and elevated serum $25(OH)D_3$ 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, $1,25(OH)_2D_3$ (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 $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$. 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 $25(OH)D_3$ to $1,25(OH)_2D_3$, has been reported in mouse 3T3-L1 preadipocytes and in adipose tissue of Wistar rats[21]. 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 $1,25(OH)_2D_3$, 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[23,61], 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 $25(OH)D_3$ to $1,25(OH)_2D_3$ has been demonstrated very recently in human mammary adipocytes, together with the release of $1,25(OH)_2D_3$ [19]. The basal and substrate-induced $1,25(OH)_2D_3$ secretion by mature adipocytes is reported to be higher than with human mammary epithelial cells; these cells are known to be highly

efficient at bioactivating $25(OH)D_3$. This finding suggests that mature adipocytes are capable of taking up $25(OH)D_3$, converting it to $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$).

Macrophages are known to play a role in vitamin D metabolism, with the ability to convert circulating $25(OH)D_3$ to $1,25(OH)_2D_3$ [62]. Adipose tissue expansion in obesity is associated with an increase in macrophage accumulation in the tissue[63,64], which may facilitate the local hydroxylation of $25(OH)D_3$. However, the specific characteristics of adipose tissue macrophages and their potential contribution to the local production of $1,25(OH)_2D_3$ need to be clarified.

Data on the actual $1,25(OH)_2D_3$ content of human adipose tissue are very limited. In a small study of seventeen morbidly obese subjects undergoing gastric bypass surgery, the $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$ 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 CCAAT/enhancer-binding protein β (C/EBPβ), followed by the expression of C/EBPα, PPARγ and sterol-regulatory element-binding protein 1 (SREBP1)[66]. As a result, there is increased expression of genes that produce the adipocyte phenotype, such as lipoprotein lipase, and adipocyte lipid-binding protein 2, which serves as a late marker of adipogenesis[67,68]. During differentiation, the expression of genes encoding lipogenic enzymes such as fatty acid synthase is highly induced and *de novo* fatty acid synthesis increases enormously[69].

There is some evidence that $1,25(OH)_2D_3$ inhibits 3T3-L1 preadipocyte differentiation in a dose-dependent manner, and this is in line with its inhibitory effect on the expression of adipogenic transcription factor (*C/EBPβ*, *PPARγ* and *SREBP1*) genes and of the downstream adipocyte markers (lipoprotein lipase, adipocyte lipid-binding protein 2 and fatty acid synthase), although $1,25(OH)_2D_3$ does not block the induction of C/EBP[22]. The linkage between $1,25(OH)_2D_3$ and adipocyte lipogenesis has also been supported by a study which demonstrated that the hormone strongly increased mRNA levels of insulin-induced gene-2 (*Insig-2*), a factor which blocks fatty acid synthesis in mature 3T3-L1 adipocytes and inhibits preadipocyte differentiation[70]. During the differentiation of human mammary preadipocytes, exposure to $25(OH)D_3$ or $1,25(OH)_2D_3$ led to a significant reduction in lipid accumulation at day 7 but not at day 14, suggesting that vitamin D metabolites may inhibit the initiation of human preadipocyte differentiation[19]. Furthermore, in addition to reducing protein expression of C/EBPα, PPARγ and adipocyte lipid-binding protein 2 by $1,25(OH)_2D_3$ alone, the combination of $1,25(OH)_2D_3$ with genistein enhanced suppression of adipocyte lipid-binding protein 2 expression and lipid accumulation in 3T3-L1 adipocytes[71]. The effects of $1,25(OH)_2D_3$ metabolites on adipogenesis may involve VDR, as $1,25(OH)_2D_3$ combined with genistein significantly increased VDR protein expression[71].

VDR has been shown to be expressed at the early stage of adipogenesis in 3T3-L1 cells and its expression levels are maintained by $1,25(OH)_2D_3$ during the course of adipocyte differentiation[65]. In the presence of $1,25(OH)_2D_3$, VDR inhibits adipogenesis by reducing C/EBPβ mRNA and C/EBPβ nuclear protein levels at a critical stage of differentiation[65]. In addition, $1,25(OH)_2D_3$ induces the up-regulation of C/EBPβ core-repressor, eight twenty-one (ETO), which would further restrain the activity of remaining C/EBPβ[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

Vitamin D-related gene	Adipose tissue	Adipocyte
VDR	Rat adipose tissue[23] Mouse adipose tissue[57]	Mouse 3T3-L1[22,23,65,71] Human mammary adipocytes[19] Human SGBS adipocytes (and preadipocytes)[60]
CYP27B1	Rat adipose tissue[21]	Mouse 3T3-L1[21] Human mammary adipocytes[19] Human SGBS adipocytes (and preadipocytes)[60]
CYP24	–	Mouse 3T3-L1[21] Human mammary adipocytes[19] Human SGBS adipocytes (and preadipocytes)[60]
CYP2R1	–	Human SGBS adipocytes (and preadipocytes)[60]

VDR, vitamin D receptor; SGBS, Simpson–Golabii–Beymel syndrome.

in the absence of $1,25(OH)_2D_3$ [22]. 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[65]. However, *in vivo* 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[72]. 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 $1,25(OH)_2D_3$ induced a significant increase in lipoprotein lipase activity and of its mRNA level in 3T3-L1 adipocytes[61]. Concurrently, fatty acid synthase, which catalyses adipocyte lipogenesis, is down-regulated by $1,25(OH)_2D_3$ in 3T3-L1 cells[22]. However, *in vivo* 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[72]. 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[20]. 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[20].

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 (n 10) 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, substrate metabolism or the expression of genes related to fat metabolism, such as hormone-sensitive lipase, fatty acid synthase and uncoupling protein 2 in adipose tissue, despite a significant increase in serum $1,25\text{-}OH_2D_3$ levels[73]. These negative results could be due to the relatively short period (7 d) of treatment or because supplementation with cholecalciferol has little effect on healthy subjects who have adequate levels of vitamin D. Taken together, the present data are inconclusive and additional models and human studies are required to clarify the role of vitamin D metabolites in lipid metabolism.

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[74,75]. 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[57]. In a Middle-Eastern population of non-obese young subjects, serum $25(OH)D_3$ 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[76].

There is some evidence that vitamin D_3 may directly regulate adipokine expression and secretion by adipocytes. An *in vitro* study has shown that treatment with $1,25(OH)_2D_3$ (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[77]. However, a recent *in vivo* study has reported that vitamin D supplementation reduced IL-6 protein content in adipose tissue of mice fed a high-fat diet, and $1,25(OH)_2D_3$ (100 nM) inhibited LPS-induced IL-6 production by 3T3-L1 adipocytes[78]. More recently, $1,25(OH)_2D_3$ (100 nM) has been shown to inhibit the release of MCP-1 and adiponectin by human adipocytes[79]. The discrepancy between results might be due to the different doses used in these studies. Therefore, further work is needed to elucidate whether $1,25(OH)_2D_3$ 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 accummulated that $1,25(OH)_2D_3$ 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[80]. It has also been shown that $1,25(OH)_2D_3$ down-regulates the gene and protein expression of toll-like receptor (TLR) 2 and TLR-4 in human monocytes[81]. $1,25(OH)_2D_3$ also suppresses peripheral blood mononuclear cells' proliferation and induces apoptosis in peripheral blood mononuclear cells of healthy subjects and inflammatory bowel disease patients[82]. Both $1,25(OH)_2D_3$ and $25(OH)D_3$ have been shown to reduce lipopolysaccharide-induced TNF-α and IL-6 production, probably by inhibiting p38 MAPK activation in human monocytes/macrophages[83]. Conversely, $1,25(OH)_2D_3$-deficient T-cells isolated from CYP27B1 knockout mice are predisposed to overexpress IL-17[84], while VDR-null mice display a failure of T-cell homing to the gut with low levels of IL-10 in inflammatory bowel disease[85]. Furthermore, in peripheral blood mononuclear cells from type-2 diabetic patients having a proinflammatory profile, $1,25(OH)_2D_3$ is reported to act in an anti-inflammatory manner to decrease the expression of TNF-α, IL-1, IL-6 and IL-8[86]. *In vivo,* aged mice treated with vitamin D_3 showed a significant improvement in visual function by reducing retinal inflammation and amyloid-β accumulation[87].

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[88,89]. Adipose tissue inflammation, characterised by increased infiltration of macrophages and other immune cells, is a central pathological process in adipose tissue dysfunction[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 extracellular matrix remodelling from human preadipocytes and adipocytes; these factors may induce inflammation, fibrosis and insulin resistance in adipose tissue[59,92–95]. The immunoregulatory effects of $1,25(OH)_2D_3$ suggest that the hormone may also modulate the inflammatory response in adipose tissue. Very recently, we have shown that treatment with $1,25(OH)_2D_3$ (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[96]. Concurrently, an inhibitory effect of $1,25(OH)_2D_3$ on TNF-α-stimulated MCP-1 release by human adipocytes has been reported[79].

Activation of the NF-κB signalling pathway is essential in the signal transduction of proinflammatory cytokines in many cell types, including adipocytes[95,97,98]. NF-κB activation involves the degradation of IκBα protein and translocation of p65 into the nucleus[99]. Our recent work has shown that $1,25(OH)_2D_3$ can increase IκBα protein abundance in human preadipocytes[96]. Blocking of NF-κB activation by $1,25(OH)_2D_3$ has also been reported in mesangial cells, as $1,25(OH)_2D_3$ can stabilise IκBα, leading to an inhibition of p65 NF-κB nuclear translocation[100]. Very recently, we have observed that $1,25(OH)_2D_3$ is able to reverse macrophage-elicited inhibition of IκBα and up-regulation of p65 NF-κB in differentiated human adipocytes (unpublished results). Overall, $1,25(OH)_2D_3$ 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[8,76,101] and children[102,103]. Higher basal levels of $25(OH)D_3$ have been found to predict better β-cell function and lower glycaemia in subjects at risk for type 2 diabetes[104]. In rats, vitamin D deficiency impairs insulin release from the pancreas and

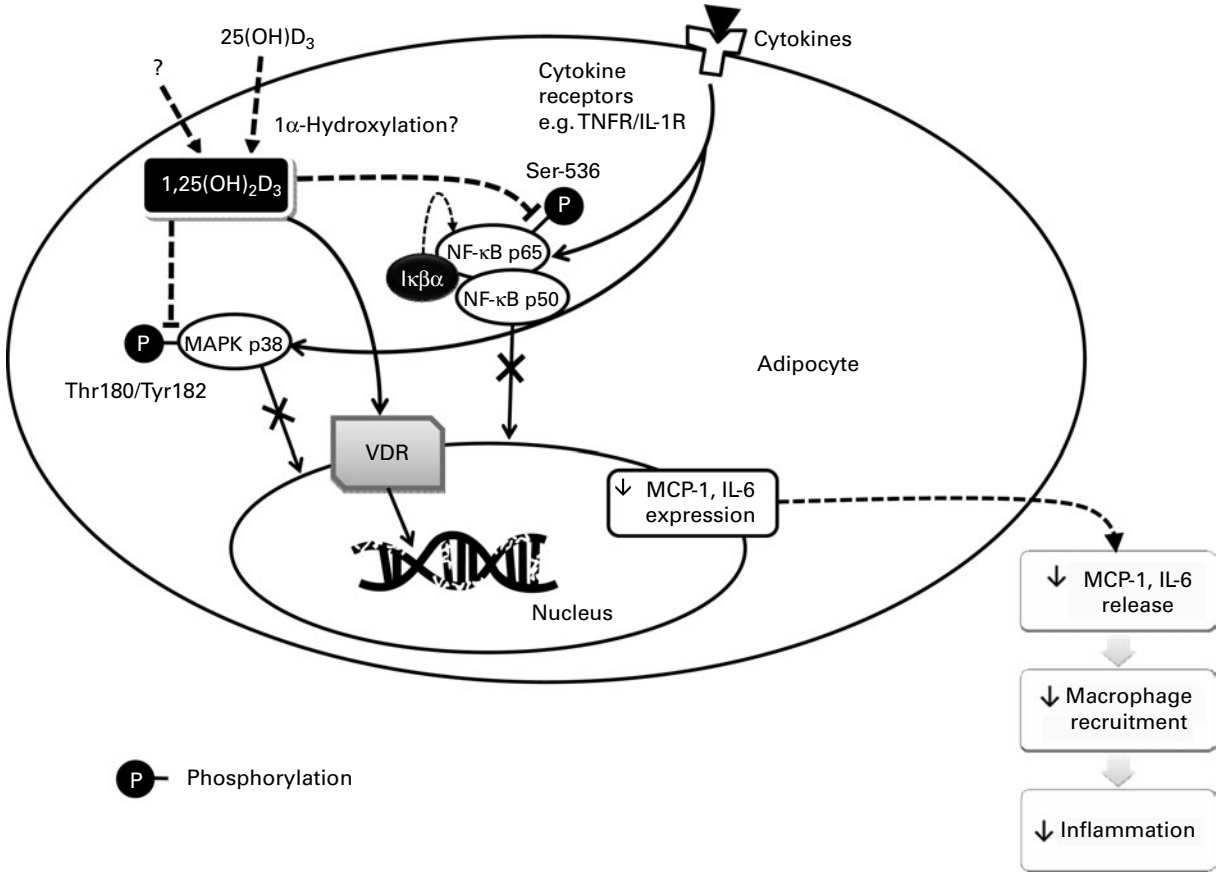

Fig. 1. Proposed mechanism of vitamin D_3 signalling in adipocytes. 1,25-Dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) may be transferred into the adipocyte (from the circulation or adjacent cells) or $25(OH)D_3$ taken up from the circulation and hydroxylated in the fat cell by 1α-hydroxylase. $1,25(OH)_2D_3$ acts to inhibit the phosphorylation of p38 MAPK and the activation of NF-κB signalling, with enhanced IκBα expression while reduced phosphorylation of p65, in human adipocytes. As a result, gene expression and protein release of proinflammatory mediators (i.e. monocyte chemoattractant protein-1 (MCP-1) and IL-6) by fat cells are reduced, leading to decreased recruitment of monocytes/macrophages and overall inflammation within adipose tissue.

reduces glucose tolerance, which is partially reversed following treatment with $1,25(OH)_2D_3$ [105,106]. 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[107]. In type 2 diabetic patients with vitamin D deficiency, daily intake of a vitamin D-fortified yogurt drink increased serum $25(OH)D_3$ levels and improved glycaemic status[108]. 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 $1,25(OH)_2D_3$ 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[109]. Adipose tissue, in addition to skeletal muscle and liver, is a key organ exhibiting insulin resistance in obesity[110]. 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[111]. In streptozotocin-induced diabetic rats, $1,25(OH)_2D_3$ treatment has been reported to normalise the number of insulin receptors and improve the insulin response to glucose transport in epididymal adipocytes[112]. 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 $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$. 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.

Acknowledgements

The authors declare that they have no conflicts of interest. C. B. and C. D. wrote the draft of the article, with subsequent additions and revisions from D. G., J. W. and P. T.; C. B. prepared the final version. The present work was supported by the Medical Research Council (G0801226) and the University of Liverpool.

References

1. Mellanby E (1976) Nutrition Classics. The Lancet **1**: 407–12, 1919. An experimental investigation of rickets. Edward Mellanby. *Nutr Rev* **34**, 338–340.
2. Boyle IT, Miravet L, Gray RW, *et al.* (1972) The response of intestinal calcium transport to 25-hydroxy and 1,25-dihydroxy vitamin D in nephrectomized rats. *Endocrinology* **90**, 605–608.
3. Tanaka Y, Frank H & DeLuca HF (1973) Biological activity of 1,25-dihydroxyvitamin D_3 in the rat. *Endocrinology* **92**, 417–422.
4. Liu PT, Stenger S, Li H, *et al.* (2006) Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* **311**, 1770–1773.
5. Wang TT, Nestel FP, Bourdeau V, *et al.* (2004) Cutting edge: 1,25-dihydroxyvitamin D_3 is a direct inducer of antimicrobial peptide gene expression. *J Immunol* **173**, 2909–2912.
6. Chen S, Law CS, Grigsby CL, *et al.* (2011) Cardiomyocyte-specific deletion of the vitamin D receptor gene results in cardiac hypertrophy. *Circulation* **124**, 1838–1847.
7. Zhang Y, Kong J, Deb DK, *et al.* (2010) Vitamin D receptor attenuates renal fibrosis by suppressing the renin–angiotensin system. *J Am Soc Nephrol* **21**, 966–973.
8. Chiu KC, Chu A, Go VLW, *et al.* (2004) Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr* **79**, 820–825.
9. Vrieling A, Hein R, Abbas S, *et al.* (2011) Serum 25-hydroxyvitamin D and postmenopausal breast cancer survival: a prospective patient cohort study. *Breast Cancer Res* **13**, R74.
10. Barchetta I, Angelico F, Del Ben M, *et al.* (2011) Strong association between non alcoholic fatty liver disease (NAFLD) and low 25(OH) vitamin D levels in an adult population with normal serum liver enzymes. *BMC Med* **9**, 85.
11. Osei K (2010) 25-OH vitamin D: is it the universal panacea for metabolic syndrome and type 2 diabetes? *J Clin Endocrinol Metab* **95**, 4220–4222.
12. Bell NH, Epstein S, Greene A, *et al.* (1985) Evidence for alteration of the vitamin D-endocrine system in obese subjects. *J Clin Invest* **76**, 370–373.
13. Wortsman J, Matsuoka LY, Chen TC, *et al.* (2000) Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* **72**, 690–693.
14. Parikh SJ, Edelman M, Uwaifo GI, *et al.* (2004) The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. *J Clin Endocrinol Metab* **89**, 1196–1199.
15. Snijder MB, van Dam RM, Visser M, *et al.* (2005) Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. *J Clin Endocrinol Metab* **90**, 4119–4123.
16. Botella-Carretero JI, Alvarez-Blasco F, Villafruela JJ, *et al.* (2007) Vitamin D deficiency is associated with the metabolic syndrome in morbid obesity. *Clin Nutr* **26**, 573–580.

British Journal of Nutrition

17. Goldner WS, Stoner JA, Thompson J, *et al.* (2008) Prevalence of vitamin D insufficiency and deficiency in morbidly obese patients: a comparison with non-obese controls. *Obes Surg* **18**, 145–150.
18. Blum M, Dolnikowski G, Seyoum E, *et al.* (2008) Vitamin D(3) in fat tissue. *Endocrine* **33**, 90–94.
19. Ching S, Kashinkunti S, Niehaus MD, *et al.* (2011) Mammary adipocytes bioactivate 25-hydroxyvitamin D and signal via vitamin D receptor, modulating mammary epithelial cell growth. *J Cell Biochem* **112**, 3393–3405.
20. Wong KE, Kong J, Zhang W, *et al.* (2011) Targeted expression of human vitamin D receptor in adipocytes decreases energy expenditure and induces obesity in mice. *J Biol Chem* **286**, 33804–33810.
21. Li J, Byrne ME, Chang E, *et al.* (2008) 1Alpha,25-dihydroxyvitamin D hydroxylase in adipocytes. *J Steroid Biochem Mol Biol* **112**, 122–126.
22. Kong J & Li YC (2006) Molecular mechanism of 1,25-dihydroxyvitamin D_3 inhibition of adipogenesis in 3T3-L1 cells. *Am J Physiol Endocrinol Metab* **290**, E916–E924.
23. Kamei Y, Kawada T, Kazuki R, *et al.* (1993) Vitamin D receptor gene expression is up-regulated by 1,25-dihydroxyvitamin D3 in 3T3-L1 preadipocytes. *Biochem Biophys Res Commun* **193**, 948–955.
24. Windaus A, Linsert O, Lüttringhaus A, *et al.* (1932) Über das krystallisierte Vitamin D_2 (About the crystallized vitamin D_2). *Justus Liebigs Annalen der Chemie* **492**, 226–241.
25. Windaus A, Schenck F & von Weder F (1936) Uber das antirachitisch wirksame bestrahlungs-produkt aus 7-dehydrocholesterin (About the anti-rachitic effective irradiation-product of 7-dehydro-cholesterol). *Hoppe-Seylers Z Physiol Chem* **241**, 100–103.
26. Masuda S, Byford V, Arabian A, *et al.* (2005) Altered pharmacokinetics of 1alpha,25-dihydroxyvitamin D_3 and 25-hydroxyvitamin D_3 in the blood and tissues of the 25-hydroxyvitamin D-24-hydroxylase (Cyp24a1) null mouse. *Endocrinology* **146**, 825–834.
27. Xu Y, Hashizume T, Shuhart MC, *et al.* (2006) Intestinal and hepatic CYP3A4 catalyze hydroxylation of 1alpha,25-dihydroxyvitamin D(3): implications for drug-induced osteomalacia. *Mol Pharmacol* **69**, 56–65.
28. Jones G, Strugnell SA & DeLuca HF (1998) Current understanding of the molecular actions of vitamin D. *Physiol Rev* **78**, 1193–1231.
29. Demay MB (2006) Mechanism of vitamin D receptor action. *Ann N Y Acad Sci* **1068**, 204–213.
30. Mangelsdorf DJ, Thummel C, Beato M, *et al.* (1995) The nuclear receptor superfamily: the second decade. *Cell* **83**, 835–839.
31. Issa LL, Leong GM & Eisman JA (1998) Molecular mechanism of vitamin D receptor action. *Inflamm Res* **47**, 451–475.
32. Carlberg C (2003) Current understanding of the function of the nuclear vitamin D receptor in response to its natural and synthetic ligands. *Recent Results Cancer Res* **164**, 29–42.
33. Sutton ALM & MacDonald PN (2003) Vitamin D: more than a "bone-a-fide" hormone. *Mol Endocrinol* **17**, 777–791.
34. Huhtakangas JA, Olivera CJ, Bishop JE, *et al.* (2004) The vitamin D receptor is present in caveolae-enriched plasma membranes and binds $1\alpha,25(OH)_2$-vitamin D_3 *in vivo* and *in vitro*. *Mol Endocrinol* **18**, 2660–2671.
35. Norman AW (2006) Minireview: vitamin D receptor: new assignments for an already busy receptor. *Endocrinology* **147**, 5542–5548.
36. Plum LA & DeLuca HF (2010) Vitamin D, disease and therapeutic opportunities. *Nat Rev Drug Discov* **9**, 941–955.
37. Dretakis OE, Tsatsanis C, Fyrgadis A, *et al.* (2010) Correlation between serum 25-hydroxyvitamin D levels and quadriceps muscle strength in elderly Cretans. *J Int Med Res* **38**, 1824–1834.
38. Baz-Hecht M & Goldfine AB (2010) The impact of vitamin D deficiency on diabetes and cardiovascular risk. *Curr Opin Endocrinol Diabetes Obes* **17**, 113–119.
39. Yiu YF, Chan YH, Yiu KH, *et al.* (2011) Vitamin D deficiency is associated with depletion of circulating endothelial progenitor cells and endothelial dysfunction in patients with type 2 diabetes. *J Clin Endocrinol Metab* **96**, E830–E835.
40. Barth JH, Butler GE, Hammond PJ. (2008) Hypercalcaemia. In *Biochemical Investigations in Laboratory Medicine. Leeds Teaching Hospitals*. www.pathology.leedsth.nhs.uk
41. Jones G (2008) Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr* **88**, 582S–586S.
42. Holick MF (2009) Vitamin D status: measurement, interpretation, and clinical application. *Ann Epidemiol* **19**, 73–78.
43. Holick MF (2011) Vitamin D: evolutionary, physiological and health perspectives. *Curr Drug Targets* **12**, 4–18.
44. Dawson-Hughes B, Heaney RP, Holick MF, *et al.* (2005) Estimates of optimal vitamin D status. *Osteoporos Int* **16**, 713–716.
45. Khandalavala BN, Hibma PP & Fang X (2010) Prevalence and persistence of vitamin D deficiency in biliopancreatic diversion patients: a retrospective study. *Obes Surg* **20**, 881–884.
46. Fish E, Beverstein G, Olson D, *et al.* (2010) Vitamin D status of morbidly obese bariatric surgery patients. *J Surg Res* **164**, 198–202.
47. Ford ES, Ajani UA, McGuire LC, *et al.* (2005) Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. *Diabetes Care* **28**, 1228–1230.
48. Konradsen S, Ag H, Lindberg F, *et al.* (2008) Serum 1,25-dihydroxy vitamin D is inversely associated with body mass index. *Eur J Nutr* **47**, 87–91.
49. Cheng S, Massaro JM, Fox CS, *et al.* (2010) Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study. *Diabetes* **59**, 242–248.
50. Rajakumar K, de las Heras J, Chen TC, *et al.* (2011) Vitamin D status, adiposity, and lipids in black American and Caucasian children. *J Clin Endocrinol Metab* **96**, 1560–1567.
51. Jorde R, Sneve M, Emaus N, *et al.* (2010) Cross-sectional and longitudinal relation between serum 25-hydroxyvitamin D and body mass index: the Tromso study. *Eur J Nutr* **49**, 401–407.
52. Freedman BI, Wagenknecht LE, Hairston KG, *et al.* (2010) Vitamin D, adiposity, and calcified atherosclerotic plaque in African-Americans. *J Clin Endocrinol Metab* **95**, 1076–1083.
53. Caron-Jobin M, Morisset AS, Tremblay A, *et al.* (2011) Elevated serum 25(OH)D concentrations, vitamin D, and calcium intakes are associated with reduced adipocyte size in women. *Obesity (Silver Spring)* **19**, 1335–1341.
54. Rosenblum JL, Castro VM, Moore CE, *et al.* (2012) Calcium and vitamin D supplementation is associated with decreased abdominal visceral adipose tissue in overweight and obese adults. *Am J Clin Nutr* **95**, 101–108.
55. Frost M, Abrahamsen B, Nielsen TL, *et al.* (2010) Vitamin D status and PTH in young men: a cross-sectional study on associations with bone mineral density, body composition and glucose metabolism. *Clin Endocrinol (Oxf)* **73**, 573–580.
56. Kayaniyil S, Vieth R, Harris SB, *et al.* (2011) Association of 25(OH)D and PTH with metabolic syndrome and its

British Journal of Nutrition

traditional and nontraditional components. *J Clin Endocrinol Metab* **96**, 168–175.
57. Narvaez CJ, Matthews D, Broun E, *et al.* (2009) Lean phenotype and resistance to diet-induced obesity in vitamin D receptor knockout mice correlates with induction of uncoupling protein-1 in white adipose tissue. *Endocrinology* **150**, 651–661.
58. Ochs-Balcom HM, Chennamaneni R, Millen AE, *et al.* (2011) Vitamin D receptor gene polymorphisms are associated with adiposity phenotypes. *Am J Clin Nutr* **93**, 5–10.
59. O'Hara A, Lim FL, Mazzatti DJ, *et al.* (2009) Microarray analysis identifies matrix metalloproteinases (MMPs) as key genes whose expression is up-regulated in human adipocytes by macrophage-conditioned medium. *Pflugers Arch* **458**, 1103–1114.
60. Trayhurn P, O'Hara A & Bing C (2011) Interrogation of microarray datasets indicates that macrophage-secreted factors stimulate the expression of genes associated with vitamin D metabolism (VDR and CYP27B1) in human adipocytes. *Adipobiology* **3**, 29–34.
61. Querfeld U, Hoffmann MM, Klaus G, *et al.* (1999) Antagonistic effects of vitamin D and parathyroid hormone on lipoprotein lipase in cultured adipocytes. *J Am Soc Nephrol* **10**, 2158–2164.
62. Bikle D (2009) Extra renal synthesis of 1,25-dihydroxyvitamin D and its health implications. *Clin Rev Bone Miner Metab* **7**, 114–125.
63. Xu H, Barnes GT, Yang Q, *et al.* (2003) Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* **112**, 1821–1830.
64. Weisberg SP, McCann D, Desai M, *et al.* (2003) Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* **112**, 1796–1808.
65. Blumberg JM, Tzameli I, Astapova I, *et al.* (2006) Complex role of the vitamin D receptor and its ligand in adipogenesis in 3T3-L1 Cells. *J Biol Chem* **281**, 11205–11213.
66. Mandrup S & Lane MD (1997) Regulating adipogenesis. *J Biol Chem* **272**, 5367–5370.
67. Christy RJ, Yang VW, Ntambi JM, *et al.* (1989) Differentiation-induced gene expression in 3T3-L1 preadipocytes: CCAAT/enhancer binding protein interacts with and activates the promoters of two adipocyte-specific genes. *Genes Dev* **3**, 1323–1335.
68. Dani C, Amri EZ, Bertrand B, *et al.* (1990) Expression and regulation of pOb24 and lipoprotein lipase genes during adipose conversion. *J Cell Biochem* **43**, 103–110.
69. Madsen L, Petersen RK & Kristiansen K (2005) Regulation of adipocyte differentiation and function by polyunsaturated fatty acids. *Biochim Biophys Acta* **1740**, 266–286.
70. Lee S, Lee DK, Choi E, *et al.* (2005) Identification of a functional vitamin D response element in the murine Insig-2 promoter and its potential role in the differentiation of 3T3-L1 preadipocytes. *Mol Endocrinol* **19**, 399–408.
71. Rayalam S, Della-Fera MA, Ambati S, *et al.* (2008) Enhanced effects of 1,25(OH)(2)D(3) plus genistein on adipogenesis and apoptosis in 3T3-L1 adipocytes. *Obesity (Silver Spring)* **16**, 539–546.
72. Wong KE, Szeto FL, Zhang W, *et al.* (2009) Involvement of the vitamin D receptor in energy metabolism: regulation of uncoupling proteins. *Am J Physiol Endocrinol Metab* **296**, E820–E828.
73. Boon N, Hul GB, Sicard A, *et al.* (2006) The effects of increasing serum calcitriol on energy and fat metabolism and gene expression. *Obesity (Silver Spring)* **14**, 1739–1746.
74. Trayhurn P, Bing C & Wood IS (2006) Adipose tissue and adipokines – energy regulation from the human perspective. *J Nutr* **136**, 1935S–1939S.
75. Trayhurn P & Wood IS (2004) Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr* **92**, 347–355.
76. Gannagé-Yared M-H, Chedid R, Khalife S, *et al.* (2009) Vitamin D in relation to metabolic risk factors, insulin sensitivity and adiponectin in a young middle-eastern population. *Eur J Endocrinol* **160**, 965–971.
77. Sun X & Zemel MB (2008) Calcitriol and calcium regulate cytokine production and adipocyte–macrophage crosstalk. *J Nutr Biochem* **19**, 392–399.
78. Lira FS, Rosa JC, Cunha CA, *et al.* (2011) Supplementing alpha-tocopherol (vitamin E) and vitamin D_3 in high fat diet decrease IL-6 production in murine epididymal adipose tissue and 3T3-L1 adipocytes following LPS stimulation. *Lipids Health Dis* **10**, 37.
79. Lorente-Cebrian S, Eriksson A, Dunlop T, *et al.* (2011) Differential effects of 1alpha,25-dihydroxycholecalciferol on MCP-1 and adiponectin production in human white adipocytes. *Eur J Nutr* **51**, 335–342.
80. Inoue M, Matsui T, Nishibu A, *et al.* (1998) Regulatory effects of 1alpha,25-dihydroxyvitamin D_3 on inflammatory responses in psoriasis. *Eur J Dermatol* **8**, 16–20.
81. Do JE, Kwon SY, Park S, *et al.* (2008) Effects of vitamin D on expression of Toll-like receptors of monocytes from patients with Behcet's disease. *Rheumatology (Oxford)* **47**, 840–848.
82. Martinesi M, Treves C, d'Albasio G, *et al.* (2008) Vitamin D derivatives induce apoptosis and downregulate ICAM-1 levels in peripheral blood mononuclear cells of inflammatory bowel disease patients. *Inflamm Bowel Dis* **14**, 597–604.
83. Zhang Y, Leung DY, Richers BN, *et al.* (2012) Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. *J Immunol* **188**, 2127–2135.
84. Bruce D, Yu S, Ooi JH, *et al.* (2011) Converging pathways lead to overproduction of IL-17 in the absence of vitamin D signaling. *Int Immunol* **23**, 519–528.
85. Yu S, Bruce D, Froicu M, *et al.* (2008) Failure of T cell homing, reduced CD4/CD8alphaalpha intraepithelial lymphocytes, and inflammation in the gut of vitamin D receptor KO mice. *Proc Natl Acad Sci U S A* **105**, 20834–20839.
86. Giulietti A, van Etten E, Overbergh L, *et al.* (2007) Monocytes from type 2 diabetic patients have a pro-inflammatory profile. 1,25-Dihydroxyvitamin D(3) works as anti-inflammatory. *Diabetes Res Clin Pract* **77**, 47–57.
87. Lee V, Rekhi E, Kam JH, *et al.* (2012) Vitamin D rejuvenates aging eyes by reducing inflammation, clearing amyloid beta and improving visual function. *Neurobiol Aging* **33**, 2382–2389.
88. Fontana L, Eagon JC, Trujillo ME, *et al.* (2007) Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes* **56**, 1010–1013.
89. Skurk T, Alberti-Huber C, Herder C, *et al.* (2007) Relationship between adipocyte size and adipokine expression and secretion. *J Clin Endocrinol Metab* **92**, 1023–1033.
90. Cinti S, Mitchell G, Barbatelli G, *et al.* (2005) Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J Lipid Res* **46**, 2347–2355.
91. Lolmede K, Duffaut C, Zakaroff-Girard A, *et al.* (2011) Immune cells in adipose tissue: key players in metabolic disorders. *Diabetes Metab* **37**, 283–290.

92. Lacasa D, Taleb S, Keophiphath M, *et al.* (2007) Macrophage-secreted factors impair human adipogenesis: involvement of proinflammatory state in preadipocytes. *Endocrinology* **148**, 868–877.
93. Keophiphath M, Achard V, Henegar C, *et al.* (2009) Macrophage-secreted factors promote a profibrotic phenotype in human preadipocytes. *Mol Endocrinol* **23**, 11–24.
94. Gao D, Trayhurn P & Bing C (2010) Macrophage-secreted factors inhibit ZAG expression and secretion by human adipocytes. *Mol Cell Endocrinol* **325**, 135–142.
95. Gao D & Bing C (2011) Macrophage-induced expression and release of matrix metalloproteinase 1 and 3 by human preadipocytes is mediated by IL-1β via activation of MAPK signaling. *J Cell Physiol* **226**, 2869–2880.
96. Gao D, Trayhurn P & Bing C (2012) Dihydroxyvitamin D_3 inhibits the cytokine-induced secretion of MCP-1 and reduces monocyte recruitment by human preadipocytes. *Int J Obes (Lond)* (Epublication ahead of print version 17 April 2012).
97. Fujihara CK, Antunes GR, Mattar AL, *et al.* (2007) Chronic inhibition of nuclear factor-κB attenuates renal injury in the 5/6 renal ablation model. *Am J Physiol Renal Physiol* **292**, F92–F99.
98. Chen Y, Kong J, Sun T, *et al.* (2011) 1,25-Dihydroxyvitamin D_3 suppresses inflammation-induced expression of plasminogen activator inhibitor-1 by blocking nuclear factor-κB activation. *Arch Biochem Biophys* **507**, 241–247.
99. Bonizzi G & Karin M (2004) The two NF-kappaB activation pathways and their role in innate and adaptive immunity. *Trends Immunol* **25**, 280–288.
100. Zhang Z, Yuan W, Sun L, *et al.* (2007) 1,25-Dihydroxyvitamin D_3 targeting of NF-kappaB suppresses high glucose-induced MCP-1 expression in mesangial cells. *Kidney Int* **72**, 193–201.
101. Scragg R, Holdaway I, Singh V, *et al.* (1995) Serum 25-hydroxyvitamin D_3 levels decreased in impaired glucose tolerance and diabetes mellitus. *Diabetes Res Clin Pract* **27**, 181–188.
102. Parikh S, Guo D-H, Pollock NK, *et al.* (2012) Circulating 25-hydroxyvitamin D concentrations are correlated with cardiometabolic risk among American Black and White adolescents living in a year-round sunny climate. *Diabetes Care* **35**, 1133–1138.
103. Olson ML, Maalouf NM, Oden JD, *et al.* (2012) Vitamin D deficiency in obese children and its relationship to glucose homeostasis. *J Clin Endocrinol Metab* **97**, 279–285.
104. Kayaniyil S, Retnakaran R, Harris SB, *et al.* (2011) Prospective associations of vitamin D with β-cell function and glycemia. *Diabetes* **60**, 2947–2953.
105. Billaudel BJ, Bourlon PM, Sutter BC, *et al.* (1995) Regulatory effect of 1,25-dihydroxyvitamin D_3 on insulin release and calcium handling via the phospholipid pathway in islets from vitamin D-deficient rats. *J Endocrinol Invest* **18**, 673–682.
106. Cade C & Norman AW (1987) Rapid normalization/stimulation by 1,25-dihydroxyvitamin D_3 of insulin secretion and glucose tolerance in the vitamin D-deficient rat. *Endocrinology* **120**, 1490–1497.
107. Mitri J, Dawson-Hughes B, Hu FB, *et al.* (2011) Effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J Clin Nutr* **94**, 486–494.
108. Nikooyeh B, Neyestani TR, Farvid M, *et al.* (2011) Daily consumption of vitamin D − or vitamin D + calcium-fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial. *Am J Clin Nutr* **93**, 764–771.
109. Maestro B, Molero S, Bajo S, *et al.* (2002) Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D(3). *Cell Biochem Funct* **20**, 227–232.
110. Hotamisligil GS (2000) Molecular mechanisms of insulin resistance and the role of the adipocyte. *Int J Obes Relat Metab Disord* **24**, Suppl. 4, S23–S27.
111. Smith U (2002) Impaired ('diabetic') insulin signaling and action occur in fat cells long before glucose intolerance – is insulin resistance initiated in the adipose tissue? *Int J Obes Relat Metab Disord* **26**, 897–904.
112. Calle C, Maestro B & Garcia-Arencibia M (2008) Genomic actions of 1,25-dihydroxyvitamin D_3 on insulin receptor gene expression, insulin receptor number and insulin activity in the kidney, liver and adipose tissue of streptozotocin-induced diabetic rats. *BMC Mol Biol* **9**, 65.