Vitamin D insufficiency is associated with obesity and its related metabolic diseases. Adipose tissues store and metabolize vitamin D and expression levels of vitamin D metabolizing enzymes are known to be altered in obesity. Sequestration of vitamin D in large amount of adipose tissues and low vitamin D metabolism may contribute to the vitamin D inadequacy in obesity. Vitamin D receptor is expressed in adipose tissues and vitamin D regulates multiple aspects of adipose biology including adipogenesis as well as metabolic and endocrine function of adipose tissues that can contribute to the high risk of metabolic diseases in vitamin D insufficiency. We will review current understanding of vitamin D regulation of adipose tissues functions as well as the molecular mechanisms through which vitamin D regulates adipose biology. The effects of supplementation or maintenance of vitamin D on obesity and metabolic diseases are also discussed.

Keywords: Cholecalciferol; adipogenesis; adipose function; obesity; metabolic diseases

INTRODUCTION

Obesity, a state of excess accumulation of white adipose tissues (WATs), and its associated metabolic diseases are increasing worldwide. Adipose tissues play important roles in systemic metabolism by storing and releasing energy as well as acting as endocrine organ. Adipose tissues become dysfunctional in obesity, which is characterized by hypertrophied adipocytes, elevated inflammation, hypoxia and fibrosis and reduced angiogenesis [1]. Alterations in adipose derived factors, elevated levels of fatty acids (FAs) and proinflammatory cytokines along with low level of adiponectin from higher mass of dysfunctional adipose tissues, are thought to cause or exacerbate cardiometabolic diseases in obesity.

Adipose tissues are present in multiple locations throughout an organism and largely divided into intraabdominal visceral and subcutaneous depots. The major visceral depots are omental and epiploic fat and major subcutaneous depots are the upper-body abdominal subcutaneous and the lower-body femoral and gluteal fat in humans [2]. In addition to WATs, bioenergetically more active brown adipose tissue (BAT) as well as inducible brown-like
adipocytes, beige or brite adipocytes, exist. Brown and beige/brite adipocytes contain more mitochondria and express uncoupling protein 1 (UCP1) and hence, have higher thermogenic capacity [3]. Each adipose depot has differential influence on systemic metabolism. Visceral adiposity, over and above total fat mass per se, is independently associated with metabolic complications, whereas fat accumulation in the lower-body is protective [2]. The amount of BAT or beige/brite fat is reduced in obesity and increasing their amount and activity could confer protection against obesity and its associated metabolic diseases [4].

In addition to its well-known effects on calcium homeostasis and bone metabolism, vitamin D exerts many other actions including proliferation and differentiation of cells and immunomodulatory functions [5]. In adipose tissues, vitamin D has been shown to affect adipocyte development and their metabolic and endocrine functions [6]. While obesity is associated with low vitamin D status and metabolic diseases, whether deficiency of vitamin D predisposes to obesity or vitamin D supplementation improves obesity and metabolic diseases is not clear. We will review vitamin D regulation of adipose biology including adipose tissue development and metabolic and endocrine properties with emphasis on molecular mechanisms that link low vitamin D status with obesity and metabolic diseases. We also discuss the effects of supplementation or maintenance of vitamin D on obesity and metabolic diseases.

VITAMIN D METABOLISM AND BIOLOGICAL FUNCTION

Vitamin D metabolism
Vitamin D is synthesized from 7-dehydrocholesterol in the skin (vitamin D3) or ingested as food (both vitamin D2 and D3 forms). Ultraviolet B photons cause the photolysis of 7-dehydrocholesterol to previtamin D3, which thermally isomerizes to vitamin D3. Vitamin D (D represents D2 and/or D3) is activated through 2 hydroxylation steps (Fig. 1). In the liver, vitamin D is hydroxylated to 25-hydroxyvitamin D [25(OH)D] by 25-hydroxylases (CYP2R1, CYP27A1, CYP3A4, CYP2J2) [7]. 25(OH)D is then activated to 1,25 dihydroxyvitamin D [1,25(OH)2D] by 1α-hydroxylase (CYP27B1) in the kidneys. Vitamin D binding protein is the specific chaperone for vitamin D and its metabolites in the blood and then to the storage sites (adipose tissues and skeletal muscle) or target tissues (liver, kidneys or parathyroid gland) and cells (monocytes and macrophages). Both 25(OH)D and 1,25(OH)2D are hydroxylated by 24-hydroxylase (CYP24A1) and degraded. Other tissues including adipose tissues also express 1α-hydroxylase and 25-hydroxylase and can activate vitamin D locally [8].

Biological functions of vitamin D
In addition to regulation of calcium homeostasis and bone metabolism, vitamin D regulates broad biological processes including proliferation, differentiation and maturation of cells, immune functions and cellular metabolism. We refer to other reviews for the roles of vitamin D and we will briefly describe the molecular details through which vitamin D regulates cellular actions.

Most of biological actions of 1,25(OH)2D3 are thought to be mediated through its nuclear receptor, vitamin D receptor (VDR) (Fig. 2). Ligand bound VDR translocates into the nucleus as a heterocomplex with retinoid X receptor and controls gene transcription by binding to vitamin D response elements of genes [9]. Through interactions with other nuclear receptors including nuclear factor kappa B (NF-κB), SPI and STAT5 vitamin D controls transcription of genes. 1,25(OH)2D3-VDR regulates hundreds of genes in cell- and tissue-specific manners [10].
VDR localizes in the caveolae structures of plasma membrane where it exerts rapid membrane-initiated signaling responses that are referred as non-genomic actions of vitamin D [11] (Fig. 2). Once bound to vitamin D, VDR interacts with plasma membrane proteins including phospholipase A2, phosphatidylinositol-3 kinase and calcium transporters. These lead to generation of secondary messengers, Ca^{2+}, cyclic adenosine monophosphate, and phosphatidylinositol 3,4,5 triphosphate (PIP3) and activation of downstream protein kinase A, protein kinase C, mitogen activated protein kinases (MAPKs) and Ca^{2+}-calmodulin kinase II [11]. Through these signaling events, vitamin D is known to affect many cellular responses. These signaling events can also lead to control of gene expression through modulation of transcriptional machinery.

VDR is present in mitochondria where 1,25(OH)_{2}D_{3} is known to negatively affect respiratory capacity in multiple cell types including platelets and keratinocytes [12,13]. Vitamin D can also inhibit cell respiration through the nuclear VDR-mediated suppression of transcription of mitochondrial respiratory chain complexes. Through regulation of mitochondrial
respiratory capacity, 1,25(OH)\textsubscript{2}D\textsubscript{3}-VDR may affect cell growth, proliferation and differentiation as well as biosynthetic pathways, especially lipid biosynthesis, as it provides bioenergetics required for the processes [13].

**Vitamin D metabolism in adipose tissues**

Vitamin D accumulates in adipose tissues and skeletal muscle and adipose tissue is thought to be the major site of vitamin D storage [14]. Slow releases from adipose tissues, however, suggest that adipose tissues may function as a vitamin D buffering system preventing uncontrolled synthesis of the active form. Vitamin D metabolizing enzymes, 25-hydroxylase (CYP2R1, CYP27A1, CYP2J2), 1α-hydroxylase (CYP27B1) and catabolic 24-hydroxylase (CYP24A1), are expressed in adipose tissues [15-18], indicating that adipose tissues also play active roles in vitamin D metabolism contributing to the low vitamin D status in obesity.

Expression levels of 25-hydroxylase (CYP2J2) and 1α-hydroxylase (CYP27B1) are reduced in obese adipose tissues [16], whereas VDR expression is increased in obesity and is positively associated with proinflammatory cytokine expression [16-18]. Visceral than subcutaneous adipose tissues express higher levels of CYP27A1 and lower levels of CYP27B1 and CYP2J2 [16]. Furthermore, 1,25(OH)\textsubscript{2}D\textsubscript{3} increases VDR expression in visceral adipose tissues from obese but not lean subjects [17]. These data indicate that local activation of vitamin D as well as their actions in adipose tissues may differ depending on the degree of obesity and adipose depots, potentially explaining the contradictory effects of vitamin supplementation on obesity and metabolic diseases.

**VITAMIN D AND ADIPOSE BIOLOGY**

**Vitamin D regulation of adipogenesis**

Adipose tissues continuously remodel throughout a life-span and mean age of adipocytes is estimated to be about 10 years in humans [19]. Adipose tissues remodel by increasing...
the size (hypertrophy) and or number (hyperplasia) of adipocytes. Remodeling through hyperplasia is considered to be protective as newly-differentiated adipocytes are insulin sensitive and contain higher capacity to store excess energy, protecting other organs from ectopic fat deposition [20]. In contrast, hypertrophic obesity is associated with impairment in adipogenesis, high inflammation and fibrosis, markers of dysfunctional adipose tissues [21,22]. Replacing dysfunctional adipocytes during development of obesity and normal aging through new adipocyte generation is crucial for the maintenance of metabolic health. We will review current understanding of the role of vitamin D in adipogenesis.

Controversial effects of vitamin D on adipogenesis

Adipogenesis is a process through which adipose progenitors differentiate into mature adipocytes. Upon treatment with adipogenic stimuli, adipose progenitors start to express adipocyte specific genes and significant changes in morphologies occur such that cells round up and accumulate neutral lipids in the form of triacylglycerol (TAG) in lipid droplets [23]. To assess the direct effects of vitamin D on adipogenesis, the active form of vitamin D, 1,25(OH)\textsubscript{2}D\textsubscript{3}, has been added to various cell culture models including 3T3-L1, a mouse embryonic cell line, and primary cultures of adipose derived stem cells (ASCs). Results from these in vitro studies, however, are controversial depending on the experimental conditions, cell types or doses used (Fig. 3). In 3T3-L1 cells, 1,25(OH)\textsubscript{2}D\textsubscript{3} inhibits adipogenesis [24,25] while enhancing adipocyte differentiation in human and mouse ASCs [15,26,27] and in bone marrow-derived mesenchymal stem cells (BM-MSC) from mouse [26] and pigs [28]. Differences in adipogenic programs between cell types may explain the contradictory results [23].

Preadipocytes are known to express vitamin D metabolizing enzymes and locally activated 1,25(OH)\textsubscript{2}D\textsubscript{3} may also modulate adipogenesis. We demonstrated that 25(OH)D\textsubscript{3} increases the expression levels of CYP24A1, a primary target of nuclear VDR, and enhances adipogenesis in human ASCs, indicating that they can generate the active form of vitamin D from 25(OH)D\textsubscript{3} [15]. Consistent with this idea, we detected 1,25(OH)\textsubscript{2}D\textsubscript{3} in the culture media when human ASCs are incubated with 25(OH)D\textsubscript{3} [15]. Vitamin D did not increase CYP24A1 expression, suggesting that 25-hydroxylase may not be functional in human ASCs.

Molecular mechanisms through which 25(OH)D\textsubscript{3} regulates adipogenesis

Both pro-adipogenic and anti-adipogenic actions of vitamin D are known to be mediated through the VDR. Kong et al. [25] showed that 1,25(OH)\textsubscript{2}D\textsubscript{3} inhibits adipogenesis through the VDR-dependent suppression of PPAR\(\gamma\), the master regulator of adipogenesis, in 3T3-L1 cells.
In contrasts, 1,25(OH)$_2$D$_3$ stimulates adipogenesis in BM-MSC derived from the wild-type, but not from VDR-knockout mice and introduction of human VDR into the knockout cells rescued the pro-adipogenic effects of 1,25(OH)$_2$D$_3$ [26]. Whether 1,25(OH)$_2$D$_3$ promotes adipogenesis in human and mouse ASCs through VDR dependent mechanisms has not been demonstrated.

Vitamin D is known to affect cell proliferation dose-dependently in both 3T3-L1 and Simpson-Golabi-Behemel Syndrome (SGBS) cells, a primary human preadipocytes obtained from subjects with SGBS [27,29]. By inhibiting cell proliferation, vitamin D may affect adipogenesis. Consistent with this idea, 1,25(OH)$_2$D$_3$ is inhibitory when added during the earlier days of differentiation but does not affect when added during later days of adipogenesis in 3T3-L1 cells [25], a cell line that post-confluent mitotic clonal expansion is critical for their differentiation into adipocytes. On the contrary, we and others have shown that 1,25(OH)$_2$D$_3$ increases lipid accumulation by acting on the later periods of adipogenesis without affecting cell commitment in human and mouse ASCs [15,30]. 1,25(OH)$_2$D$_3$ may support the differentiated state after induction of adipogenesis is consolidated by stimulating FA biosynthesis and lipid accumulation as acetyl-CoAs are directed for synthetic pathway from oxidation in mitochondria [13].

Lessons learned from mouse models
To understand roles of vitamin D and VDR in the regulation of adiposity in vivo, animal models have been used. Reduced vitamin D signaling through global knockout of 1α-hydroxylase (CYP27B1) and VDR in mice leads to a lean phenotype when fed a high-fat diet or high-calcium rescue diet [31,32]. In contrast, adipocyte-VDR null mice are fatter with sex-specific effects such that female but not male adipocyte-VDR knockout mice exhibit higher growth rates and increased visceral fat mass [33]. These studies imply that the lower fat mass in the global VDR knockout models may not be due to the direct effects of vitamin D on adipocytes. However, transgenic mice overexpressing human VDR in adipose tissues are fatter and exhibit reduced energy metabolism without alterations in food intake [34], consistent with the phenotypes of the global knockout mice.

The lean phenotype and defective cellular adipogenesis in the VDR-null mice become apparent with age [32] and reduction in adipocyte size is observed in older (1 year) but not in young (21 days) mice [35]. Further, maternal vitamin D deficiency does not impact adipose tissue development in offspring [35,36]. These results indicate that deficiency of VDR does not affect fat deposition during early development. Age-associated lean phenotype in the VDR-null mice may be due to the fact that 1,25(OH)$_2$D$_3$-VDR decreases energy expenditure through uncoupling process [13] and age-associated alopecia [35].

Role of vitamin D in adipose tissue function
Adipocytes store excess energy in the form of TAG and release them as FAs and glycerol when body energy demands increase during fasting or exercise. Adipose tissues are also endocrine organs secreting number of peptide hormones and cytokines including leptin, adiponectin and interleukin (IL)-6. By acting as both metabolic and endocrine organs, adipose tissues play crucial roles in energy homeostasis and alterations in adipose derived metabolic and endocrine products are thought to cause or exacerbate insulin resistance and other cardiometabolic diseases in obesity [20].

Effects of vitamin D on adipose metabolic functions
The amount of TAG storage in adipocytes is governed by the balance of lipid synthesis and breakdown. The role of vitamin D in adipocyte lipid metabolism is relatively unknown.
An earlier study by Shi et al. [30] reported that 1,25(OH)\textsubscript{2}D\textsubscript{3} stimulates calcium influx into adipocytes affecting lipid metabolism through the membrane bound VDR. Similarly, more recent studies showed that 1,25(OH)\textsubscript{2}D\textsubscript{3} reduced TAG accumulation by increasing basal and adrenergically stimulated lipolysis [37] and decreasing de novo lipogenesis in 3T3-L1 adipocytes [38]. 1,25(OH)\textsubscript{2}D\textsubscript{3} stimulates mRNA expression of several genes related to FA oxidation including CPT1A, PGC1\textalpha and PPAR\textalpha as well as UCP1 [37] and rates of FA oxidation in 3T3-L1 adipocytes [38]. Overall, these data suggest that 1,25(OH)\textsubscript{2}D\textsubscript{3} has catabolic effects in adipocytes decreasing lipid accumulation, which could potentially reduce the size of adipocytes [Fig. 4A]. The non-genomic actions of vitamin D through calcium influx [30] may also explain the fact that calcium supplementation alone corrects most of the changes mediated by vitamin D deficiency in rats [39].

The phenotypes of VDR-null and overexpression transgenic mice do not support these catabolic effects of vitamin D on adipocyte lipid metabolism [Fig. 4B]. Both VDR and 1α-hydroxylase (CYP27B1) knockout mice are lean and express higher levels of UCP1 in both white and brown fat and exhibit elevated levels of beta oxidation in WAT [31,32]. Further, overexpression of human VDR in mouse adipose tissues reduced expression of genes involved in the regulation of FA transport, thermogenesis, and lipolysis and suppressed FA oxidation and lipolysis [34]. Some of these phenotypes may have been mediated by indirect catabolic effects of VDR on whole body energy homeostasis [13,35].

Vitamin D is known to affect insulin actions and glucose metabolism in adipocytes. 1,25(OH)\textsubscript{2}D\textsubscript{3} enhances insulin-stimulated AKT phosphorylation, GLUT4 translocation and glucose transport in 3T3-L1 adipocytes [40,41]. In addition, vitamin D supplementation stimulates glucose uptake in adipose tissue of high fat diet-fed mice [42]. Results from transcriptome analysis in human adipocytes show that vitamin D increases oxidative stress [43], suggesting that it may impair insulin signaling pathway. Further studies of dissecting the role of vitamin D and VDR in human adipocyte metabolism are warranted.

**Effects of vitamin D on adipose inflammation and endocrine function**

Anti-inflammatory actions of vitamin D are well-known and most of studies showed that vitamin D decreases inflammation in adipose tissues. In both preadipocytes and adipocytes, 1,25(OH)\textsubscript{2}D\textsubscript{3} suppresses expression levels of multiple cytokines including IL-6, IL-1\beta, IL-8, macrophage chemoattractant protein-1 and leptin [40,41,44-49]. Further, 1,25(OH)\textsubscript{2}D\textsubscript{3}
stimulate adiponectin, an anti-inflammatory and insulin sensitizing adipokine, in 3T3-L1 adipocytes [41]. Contradictory results showing vitamin D increasing IL-6 and IL-8 in adipocytes [10] and leptin in mouse adipose tissues [50] have been also reported.

1,25(OH)₂D₃ decreases cytokines through the VDR in 3T3-L1 adipocytes [40] and in preliminary experiments, we found that 1,25(OH)₂D₃ suppresses proinflammatory cytokines through the VDR-dependent mechanisms in human adipocytes (unpublished observation, Nimithphong H and Lee MJ). Further, 1,25(OH)₂D₃ increases mRNA expression levels of dual specificity protein 10 and IkBα and inhibits NF-κB and p38 MAPK signaling pathways in 3T3-L1 adipocytes [40]. The proinflammatory actions of 1,25(OH)₂D₃ in 3T3-L1 adipocytes are known to be mediated through non-genomic actions of VDR in calcium signaling pathway [10].

Adipose tissues contain other cells including several types of immune cells and endothelial cells. In immune cells, vitamin D inhibits cytokine expression through the VDR-mediated suppression of proinflammatory NF-κB and MAPK signaling pathways [51,52]. By suppressing chemokine production from multiple cell types, vitamin D-VDR blocks monocyte migration into adipose tissues, as demonstrated in mouse models in vivo [48]. In addition, 1,25(OH)₂D₃ also regulates the function of macrophages and other immune cell populations within adipose tissues [53,54]. Overall, these results from in vitro studies and in vivo mouse models support that the anti-inflammatory actions of vitamin D in adipose tissues. By suppressing adipose tissue inflammation, vitamin D could improve systemic metabolism in obesity.

The in vivo effects of supplementation of vitamin D on serum levels of inflammatory cytokines in humans are controversial. Meta-analysis of vitamin D supplementation in obese and overweight subjects with mean baseline 25(OH)D levels from 12 to 32.6 ng/mL reported no significant changes in C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α) and IL-6 concentrations [55]. Another meta-analysis in 484 subjects with obese/overweight with or without type 2 diabetes also reported no significant effect of vitamin D supplementation on adiponectin and leptin levels [56]. On the contrary, a recent meta-analysis of 6 clinical trials with a mean baseline 25(OH)D of 24 ng/mL showed that vitamin D supplementation significantly increased serum leptin with a pool mean difference of about 5 ng/mL [57]. In a systematic review and meta-analysis, Yu et al. [58] reported that vitamin D supplementation significantly decreased CRP levels by 0.45 μg/mL without affecting TNF-α and IL-6, when studies in type 2 diabetes were exclusively considered. Therefore, different doses, duration and populations employed between studies may have contributed to the contradictory results.

**LOW VITAMIN D STATUS IN OBESITY AND METABOLIC DISEASES**

Vitamin D status is assessed by serum 25(OH)D as levels of 1,25(OH)₂D do not reflect vitamin D status [59]. Vitamin D status is influenced by diets, sun exposure, races, and genetic factors and the optimal serum 25(OH)D level for skeletal health is accepted to be above 20 ng/mL by the Institute of Medicine [60] or 30 ng/mL by the National Osteoporosis Foundation [61] and the International Osteoporosis Foundation [62].

Numerous studies have shown that low vitamin D status is associated with obesity and metabolic diseases [16-18,63-65]. Several factors including lower vitamin D intake and sun
exposure have been proposed to explain the lower vitamin D status in obesity. Others suggest that reduced serum levels are caused by both sequestration and volumetric dilution of vitamin D in larger amount of adipose tissues in obesity [66,67]. Lower expression levels of \textit{CYP2J2} and \textit{CYP27B1} in adipose tissues [16] may also contribute to the vitamin D inadequacy in obesity.

**Clinical effects of vitamin D supplementation on obesity**

Interventional studies of vitamin D supplementation and adiposity measures and metabolic diseases remain inconclusive. We summarize results from human studies that had primary or secondary objectives to investigate the effect of vitamin D supplementation on obesity and metabolic diseases. In a systemic review and meta-analysis of 12 randomized controlled trials (RCTs) that had supplemented vitamin D without caloric restriction [68], Pathak et al. [68] showed that supplementation of various doses of vitamin D for 6 to 52 weeks resulted in neutral effects on standardized mean difference for body weight, fat mass, % fat mass or lean body mass. Another systemic review and meta-analysis investigated the effects of vitamin D supplementation alone (vitamin D$_3$ in all except for one that used vitamin D$_2$ and another that used alpha-calcidiol) or with calcium on adiposity measures [69]. This analysis included 26 RCTs and 42,430 participants with median treatment duration of 12 months and found no significant effects of vitamin D supplementation, compared to placebo or calcium control, on body mass index (BMI), body weight or fat mass. However, vitamin D plus calcium compared to placebo showed a small but significant reduction in body weight without effects on BMI or fat mass. The significant reduction in body weight was largely driven by the inclusion of the Women’s Health Initiative Calcium/Vitamin D Supplemental Trial [70]. Of note, only changes in body weight, but not BMI and fat mass, were reported in the trial. An analysis for a dose-response effect by vitamin D$_3$, from < 1,000 IU/day to > 4,000 IU/day, revealed no effect on any of the adiposity outcomes in any dosage groups [69].

Since those 2 reviews were published, there have been 6 RCTs that examined the effects of vitamin D supplementation on adiposity [71-76]. Results from these studies also do not support the role of vitamin D in reducing adiposity. Further, in a bi-directional genetic approach using Mendelian randomization to limit confounding, Vimaleswaran et al. [77] showed that although a higher BMI was causally related to lower 25(OH)D, vitamin D deficiency was not a causal factor for the development of obesity. Therefore, RCTs of vitamin D supplementation have not provided evidence of cause-effect relation between vitamin D status and body weight control.

**Clinical effects of vitamin D on metabolic disorders**

A meta-analysis consisted of 1,181 individuals with BMI > 23 kg/m$^2$ and normal or impaired fasting glucose levels showed that vitamin D and/or calcium supplementation has no significant effect on fasting glucose and insulin levels as well as homeostatic model assessment-insulin resistance (HOMA-IR) index [78]. Importantly, the results were similar when the supplemented doses (low dose: 125–2,000 IU/day vs. high dose: 3,571–4,000 IU/day), durations of supplementation (short: until 15-weeks vs. long: > 15 weeks) or baseline of 25(OH)D concentrations (deficiency: < 50 nmol/L [20 ng/mL] vs. insufficiency: 52.5–72.5 nmol/L [21–30 ng/mL]) were taken under consideration in subgroup-analysis. Similarly, in a recent systematic quantitative review on findings from meta-analyses, Rejnmark et al. [79] also showed null-findings in the risk of cardiometabolic diseases with vitamin D supplementation. A meta-analysis of 24 RCTs, however, showed that a significant reduction in HbA1c, fasting plasma glucose and HOMA-IR following vitamin D supplementation in type 2 diabetic patients [80]. The authors suggest that a minimum dose of 4,000 IU/
day of vitamin D which brings serum 25(OH)D values to higher than 100 nmol/L (40 ng/mL) may be recommended as an adjunct therapy to improve glycemic measures in type 2 diabetic patients. In addition, combined supplementation of calcium plus vitamin D for eight weeks significantly improved glucose and lipid metabolism in overweight to obese, vitamin D-deficient women with polycystic ovary syndrome [81]. Differences in study designs including doses, durations, baseline vitamin D status and study subjects may explain contradictory results and more studies investigating in a specific group of participants with or without true vitamin D deficiency are needed.

CONCLUSION

Adipose tissues act as a storage or buffering site of vitamin D but also participate vitamin D metabolism. Vitamin D affects new fat cell formation as well as metabolic and endocrine functions of adipose tissues. Results from cell culture and mouse models assessing the role of vitamin D in adipogenesis are inconsistent. Both suppression and promotion of adipogenesis have been reported depending on the cell culture models and conditions used. Both CYP27B1 and VDR knockout mice are lean while transgenic mice overexpressing human VDR in adipocytes are obese, supporting the positive actions of vitamin D-VDR on adipogenesis in vivo. However, results from more careful studies suggest that the phenotypes of the transgenic mice are due to vitamin D actions on systemic energy metabolism, rather than direct effects on adipocyte development. Although vitamin D actions on adipose metabolism are relatively unknown, several studies show that it regulates lipolysis and lipid synthesis and improve insulin signaling pathways. In addition, vitamin D may improve adipose tissue inflammation. These results suggest that vitamin D may ameliorate adipose tissue dysfunctions, linking low vitamin D status to metabolic disease in obesity as shown in many association studies. Whether maintenance or restoration of vitamin D status has beneficial effects on systemic metabolism is not known and more studies are warranted to establish a causal relationship. Further elucidation of the role of vitamin D and mechanisms through which vitamin D regulates adipose biology may lead to discovery of therapeutics to improve metabolic health in obesity.

REFERENCES

1. Crewe C, An YA, Scherer PE. The ominous triad of adipose tissue dysfunction: inflammation, fibrosis, and impaired angiogenesis. J Clin Invest 2017;127:74-82.
   [PUBMED] [CROSSREF]
2. Lee MJ, Wu Y, Fried SK. Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications. Mol Aspects Med 2013;34:141.
   [PUBMED] [CROSSREF]
3. Shabalina IG, Petrovic N, de Jong JM, Kalinovich AV, Cannon B, Nedergaard J. UCP1 in brite/beige adipose tissue mitochondria is functionally thermogenic. Cell Reports 2013;5:1196-203.
   [PUBMED] [CROSSREF]
4. Yoneshiro T, Saito M. Activation and recruitment of brown adipose tissue as anti-obesity regimens in humans. Ann Med 2015;47:133-41.
   [PUBMED] [CROSSREF]
5. Umar M, Sastry KS, Choucane AI. Role of vitamin D beyond the skeletal function: a review of the molecular and clinical studies. Int J Mol Sci 2018;19:1618.
   [PUBMED] [CROSSREF]
6. Mutt SJ, Hyypönen E, Saarnio J, Järvelin MR, Herzig KH. Vitamin D and adipose tissue-more than storage. Front Physiol 2014;5:228.
   [PUBMED] [CROSSREF]
1. Thacher TD, Levine MA. CYP2R1 mutations causing vitamin D-deficiency rickets. J Steroid Biochem Mol Biol 2017;173:333-6.
2. Bouillon B, Marcocci C, Carmeliet G, Bijl KE, White JH, Dawson-Hughes B, Lips P, Munns CF, Lazaretti-Castro M, Giustina A, Bilezikian J. Skeletal and extraskeletal actions of vitamin D: current evidence and outstanding questions. Endocr Rev 2019;40:1109-51.
3. Fleet JC, DeSmet M, Johnson R, Li Y. Vitamin D and cancer: a review of molecular mechanisms. Biochem J 2012;441:61-76.
4. Sun X, Zemel MB. Calcium and 1,25-dihydroxyvitamin D3 regulation of adipokine expression. Obesity (Silver Spring) 2007;15:340-8.
5. Hii CS, Ferrante A. The non-genomic actions of vitamin D. Nutrients 2016;8:135.
6. Silvagno F, Consiglio M, Foglizzo V, Destefanis M, Pescarmona G. Mitochondrial translocation of vitamin D receptor is mediated by the permeability transition pore in human keratinocyte cell line. PLoS One 2013;8:e54716.
7. Silvagno F, Pescarmona G. Spotlight on vitamin D receptor, lipid metabolism and mitochondria: Some preliminary emerging issues. Mol Cell Endocrinol 2017;450:24-31.
8. Rosenstreich SJ, Rich C, Volwiler W. Deposition in and release of vitamin D3 from body fat: evidence for a storage site in the rat. J Clin Invest 1971;50:679-87.
9. Nimitphong H, Holick MF, Fried SK, Lee MJ. 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 promote the differentiation of human subcutaneous preadipocytes. PLoS One 2012;7:e52171.
10. Wamberg L, Christiansen T, Paulsen SK, Fisker S, Rask P, Rejmark L, Richelsen B, Pedersen SB. Expression of vitamin D-metabolizing enzymes in human adipose tissue -- the effect of obesity and diet-induced weight loss. Int J Obes 2013;37:651-7.
11. Clemente-Postigo M, Muñoz-Garach A, Serrano M, Garrido-Sánchez L, Bernal-López MR, Fernández-García D, Moreno-Santos I, Garriga N, Castellano-Castillo D, Camargo A, Fernández-Real JM, Cardona F, Tinahones FJ, Macías-González M. Serum 25-hydroxyvitamin D and adipose tissue vitamin D receptor gene expression: relationship with obesity and type 2 diabetes. J Clin Endocrinol Metab 2015;100:E591-E597.
12. Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, Blomqvist L, Hoffstedt J, Näslund E, Britton T, Concha H, Hassan M, Rydén M, Frisén J, Arner P. Dynamics of fat cell turnover in humans. Nature 2008;453:783-7.
13. Gustafson B, Hedjazifar S, Gogg S, Hammarstedt A, Smith U. Insulin resistance and impaired adipogenesis. Trends Endocrinol Metab 2015;26:193-200.
14. Lee MJ, Pickeing RT, Shibab V, Wu Y, Karastergiou K, Jager M, Lavey MD, Fried SK. Impaired glucocorticoid suppression of TGFβ signaling in human omental adipose tissues limits adipogenesis and may promote fibrosis. Diabetes 2019;68:587-97.
15. Blumberg JM, Tzameli I, Astopova I, Lam FS, Flier JS, Hollenberg AN. Complex role of the vitamin D receptor and its ligand in adipogenesis in 3T3-L1 cells. J Biol Chem 2006;281:11205-13.
25. Kong J, Li YC. Molecular mechanism of 1,25-dihydroxyvitamin D₃ inhibition of adipogenesis in 3T3-L1 cells. Am J Physiol Endocrinol Metab 2006;290:E916-24.

26. Narvaez CJ, Simmons KM, Brunton J, Salinero A, Chittur SV, Welsh JE. Induction of STEAP4 correlates with 1,25-dihydroxyvitamin D₃ stimulation of adipogenesis in mesenchymal progenitor cells derived from human adipose tissue. J Cell Physiol 2013;228:2024-36.

27. Felicidade I, Sartori D, Coort SL, Semprebon SC, Niwa AM, D’Epiro GF, Biazi BI, Marques LA, Evelo CT, Mantovani MS, Ribeiro LR. Role of 1α,25-dihydroxyvitamin D₃ in adipogenesis of SGBS cells: new insights into human preadipocyte proliferation. Cell Physiol Biochem 2018;48:397-408.

28. Mahajan A, Stahl CH. Dihydroxy-cholecalciferol stimulates adipocytic differentiation of porcine mesenchymal stem cells. J Nutr Biochem 2009;20:512-20.

29. Nobre JL, Lisboa PC, Carvalho JC, Martins MR, Vargas S, Barja-Fidalgo C, de Moura EG, de Oliveira E. Leptin blocks the inhibitory effect of vitamin D on adipogenesis and cell proliferation in 3T3-L1 adipocytes. Gen Comp Endocrinol 2018;266:1-8.

30. Shi H, Norman AW, Okamura WH, Sen A, Zemel MB. 1α,25-Dihydroxyvitamin D₃ modulates human adipocyte metabolism via nongenomic action. FASEB J 2001;15:2751-1.

31. Wong KE, Szeto FL, Zhang W, Ye H, Kong J, Zhang Z, Sun XJ, Li YC. Involvement of the vitamin D receptor in energy metabolism: regulation of uncoupling proteins. Am J Physiol Endocrinol Metab 2009;296:E820-8.

32. Narvaez CJ, Matthews D, Broun E, Chan M, Welsh J. 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 2009;150:651-61.

33. Matthews DG, D’Angelo J, Drellich J, Welsh J. Adipose-specific VDR deletion alters body fat and enhances mammary epithelial density. J Steroid Biochem Mol Biol 2016;164:299-308.

34. Wong KE, Kong J, Zhang W, Szeto FL, Ye H, Deb DK, Brady MJ, Li YC. Targeted expression of human vitamin D receptor in adipocytes decreases energy expenditure and induces obesity in mice. J Biol Chem 2011;286:33804-10.

35. Schutkowski A, Max D, Bönn M, Brandsch C, Grundmann SM, Hirche F, Staeger MS, Stangl GI. Vitamin D does not play a functional role in adipose tissue development in rodent models. Mol Nutr Food Res 2018;62:62.

36. Belenchia AM, Jones KL, Will M, Beversdorf DQ, Vieira-Potter V, Rosenfeld CS, Peterson CA. Maternal vitamin D deficiency during pregnancy affects expression of adipogenic-regulating genes peroxisome proliferator-activated receptor gamma (PPARγ) and vitamin D receptor (VDR) in lean male mice offspring. Eur J Nutr 2018;57:723-30.

37. Chang E, Kim Y. Vitamin D decreases adipocyte lipid storage and increases NAD-SIRT1 pathway in 3T3-L1 adipocytes. Nutrition 2016;32:702-8.

38. Larrick BM, Kim KH, Donkin SS, Teegarden D. 1,25-Dihydroxyvitamin D regulates lipid metabolism and glucose utilization in differentiated 3T3-L1 adipocytes. Nutr Res 2018;58:72-83.

39. Bhat M, Noolu B, Qadri SS, Ismail A. Vitamin D deficiency decreases adiposity in rats and causes altered expression of uncoupling proteins and steroid receptor coactivator3. J Steroid Biochem Mol Biol 2014;144 Pt B:304-12.

40. Marcotorchino J, Gouranton E, Romier B, Tourniaire F, Astier J, Malezet C, Amiot MJ, Landrier JF. Vitamin D reduces the inflammatory response and restores glucose uptake in adipocytes. Mol Nutr Food Res 2012;56:1771-82.
41. Manna P, Jain SK. Vitamin D up-regulates glucose transporter 4 (GLUT4) translocation and glucose utilization mediated by cystathionine-\(\gamma\)-lyase (CSE) activation and H2S formation in 3T3L1 adipocytes. J Biol Chem 2012;287:42324-32.

42. Manna P, Achari AE, Jain SK. Vitamin D supplementation inhibits oxidative stress and upregulate SIRT1/AMPK/GLUT4 cascade in high glucose-treated 3T3L1 adipocytes and in adipose tissue of high fat diet-fed diabetic mice. Arch Biochem Biophys 2017;615:22-34.

43. Sun X, Morris KL, Zemel MB. Role of calcitriol and cortisol on human adipocyte proliferation and oxidative and inflammatory stress: a microarray study. J Nutrigenet Nutrigenomics 2008;1:30-48.

44. Lorente-Cebrián S, Eriksson A, Dunlop T, Mejhert N, Dahlman I, Aström G, Sjölin E, Wåhlén K, Carlberg C, Laurencikiene J, Hedén P, Arner P, Rydén M. Differential effects of 1α,25-dihydroxycholecalciferol on MCP-1 and adiponectin production in human white adipocytes. Eur J Nutr 2012;51:335-42.

45. Wamberg L, Cullberg KB, Rejnmark L, Richelsen B, Pedersen SB. Investigations of the anti-inflammatory effects of vitamin D in adipose tissue: results from an in vitro study and a randomized controlled trial. Horm Metab Res 2013;45:456-62.

46. Ding C, Wilding JP, Bing C. 1,25-Dihydroxyvitamin D\(\text{3}\) protects against macrophage-induced activation of NFκB and MAPK signalling and chemokine release in human adipocytes. PLoS One 2013;8:e61707.

47. Gao D, Trayhurn P, Bing C. 1,25-Dihydroxyvitamin D\(\text{3}\) inhibits the cytokine-induced secretion of MCP-1 and reduces monocyte recruitment by human preadipocytes. Int J Obes 2013;37:357-65.

48. Karkeni E, Marcotorchino J, Tourniaire F, Astier J, Peiretti F, Darmon P, Landrier JF. Vitamin D limits chemokine expression in adipocytes and macrophage migration in vitro and in male mice. Endocrinology 2015;156:1782-93.

49. Kong J, Chen Y, Zhu G, Zhao Q, Li YC. 1,25-Dihydroxyvitamin D\(\text{3}\) upregulates leptin expression in mouse adipose tissue. J Endocrinol 2013;216:265-71.

50. Sun J, Kong J, Duan Y, Szeo FL, Liao A, Madara JL, Li YC. Increased NF-κB activity in fibroblasts lacking the vitamin D receptor. Am J Physiol Endocrinol Metab 2006;291:E315-22.

51. Zhang Y, Leung DY, Richers BN, Liu Y, Remigio LK, Riches DW, Goleva E. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. J Immunol 2012;188:2127-35.

52. Chum RF, Lauridsen AL, Suon L, Zella LA, Pike JW, Modlin RL, Martineau AR, Wilkinson RJ, Adams J, Hewison M. Vitamin D-binding protein directs monocyte responses to 25-hydroxy- and 1,25-dihydroxyvitamin D. J Clin Endocrinol Metab 2010;95:3368-76.

53. Christakos S, Dhawan P, Ajibade D, Benn BS, Feng J, Joshi SS. Mechanisms involved in vitamin D mediated intestinal calcium absorption and in non-classical actions of vitamin D. J Steroid Biochem Mol Biol 2010;121:183-7.

54. Jamka M, Woźniiewicz M, Włokowiak J, Bogański P, Jeszka J, Stemach-Mardas M. The effect of vitamin D supplementation on selected inflammatory biomarkers in obese and overweight subjects: a systematic review with meta-analysis. Eur J Nutr 2016;55:2163-76.

55. Dinca M, Serban MC, Sahebkar A, Mikhailidis DP, Toth PP, Martin SS, Blaha MJ, Blüher M, Gunhan C, Penson P, Michos ED, Hernandez AV, Jones SR, Banach M. Lipid Blood Pressure Meta-analysis Collaboration LBPMC Group. Does vitamin D supplementation alter plasma adipokines concentrations? A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2016;107:360-71.
57. Hajimohammadi M, Shah-Bidar S, Neyestani TR. Vitamin D and serum leptin: a systematic review and meta-analysis of observational studies and randomized controlled trials. Eur J Clin Nutr 2017;71:1144-53.

58. Yu Y, Tian L, Xiao Y, Huang G, Zhang M. Effect of vitamin D supplementation on some inflammatory biomarkers in type 2 diabetes mellitus subjects: a systematic review and meta-analysis of randomized controlled trials. Ann Nutr Metab 2018;73:62-73.

59. Romagnoli E, Pepe J, Piemonte S, Cipriani C, Minisola S. Management of endocrine disease: value and limitations of assessing vitamin D nutritional status and advised levels of vitamin D supplementation. Eur J Endocrinol 2013;169:R59-69.

60. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96:53-8.

61. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Lindsay R; National Osteoporosis Foundation. Clinician’s guide to prevention and treatment of osteoporosis. Osteoporos Int 2014;25:2359-81.

62. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, Josse RG, Lips P, Morales-Torres J, Yoshimura N. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int 2010;21:1151-4.

63. Lenders CM, Feldman HA, Von Scheven E, Merewood A, Sweeney C, Wilson DM, Lee PD, Abrams SH, Gitelman SE, Wertz MS, Klish WJ, Taylor GA, Chen TC, Holick MF; Elizabeth Glaser Pediatric Research Network Obesity Study Group. Relation of body fat indexes to vitamin D status and deficiency among obese adolescents. Am J Clin Nutr 2009;90:459-67.

64. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988-1994 compared with 2000-2004. Am J Clin Nutr 2008;88:1519-27.

65. Valiña-Tóth AL, Lai Z, Yoo W, Abou-Samra A, Gadegbeku CA, Flack JM. Relationship of vitamin D and parathyroid hormone with obesity and body composition in African Americans. Clin Endocrinol (Oxf) 2010;72:595-603.

66. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690-3.

67. Drincic AT, Armas LA, Van Diest EE, Heaney RP. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. Obesity (Silver Spring) 2012;20:1444-8.

68. Pathak K, Soares MJ, Calton EK, Zhao Y, Hallett J. Vitamin D supplementation and body weight status: a systematic review and meta-analysis of randomized controlled trials. Obes Rev 2014;15:528-37.

69. Chandler PD, Wang L, Zhang X, Sesso HD, Moorthy MV, Obi O, Lewis J, Prince RL, Danik JS, Manson JE, LeBoff MS, Song Y. Effect of vitamin D supplementation alone or with calcium on adiposity measures: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev 2015;73:577-93.

70. Caan B, Neuhouse M, Aragaki A, Lewis CB, Jackson R, LeBoff MS, Margolis KL, Powell L, Uwaiso G, Whitlock E, Wylie-Rosett J, LaCroix A. Calcium plus vitamin D supplementation and the risk of postmenopausal weight gain. Arch Intern Med 2007;167:893-902.

71. Tuomainen TP, Virtanen JK, Vuolteenaho S, Nurmi T, Mursu J, de Mello VD, Schwab U, Hakumäki M, Pulkki K, Uusitupa M. Glucose metabolism effects of vitamin D in prediabetes: the VitDmet randomized placebo-controlled supplementation study. J Diabetes Res 2015;2015:672653.

72. Mitchell DM, Leder BZ, Cagliero E, Mendoza N, Henao MP, Hayden DL, Finkelstein JS, Burnett-Bowie SA. Insulin secretion and sensitivity in healthy adults with low vitamin D are not affected by high-dose ergocalciferol administration: a randomized controlled trial. Am J Clin Nutr 2015;102:385-92.
73. Cassity EP, Redzic M, Teager CR, Thomas DT. The effect of body composition and BMI on 25(OH)D response in vitamin D-supplemented athletes. Eur J Sport Sci 2016;16:773-9.

74. Sadiya A, Ahmed SM, Carlsson M, Tesfa Y, George M, Ali SH, Siddieg HH, Abusnana S. Vitamin D supplementation and body composition in persons with obesity and type 2 diabetes in the UAE: A randomized controlled double-blinded clinical trial. Clin Nutr 2016;35:77-82.

75. Moua A, Naderpoor N, de Courten MP, Teede H, Kello N, Walker K, Scragg R, de Courten B. Vitamin D supplementation has no effect on insulin sensitivity or secretion in vitamin D-deficient, overweight or obese adults: a randomized placebo-controlled trial. Am J Clin Nutr 2017;105:1372-81.

76. Karefylakis C, Särnblad S, Ariander A, Ehlersson G, Rask E, Rask P. Effect of vitamin D supplementation on body composition and cardiorespiratory fitness in overweight men-a randomized controlled trial. Endocrine 2018;61:388-97.

77. Vimaleswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, Cooper JD, Dastani Z, Li R, Houston DK, Wood AR, Michaelsson K, Vandenput L, Zgaga L, Yerges-Armstrong LM, McCarthy MI, Dupuis J, Kaakinen M, Kleber ME, Jameson K, Arden N, Raitakari O, Viikari J, Lohman KK, Ferrucci L, Melhus H, Ingelsson E, Byberg L, Lind L, Lorentzon M, Salomaa V, Campbell H, Dunlop M, Mitchell BD, Herzig KH, Pouta A, Hartikainen AL, Streten EA, Theodoratou E, Jula A, Wareham NJ, Ohlsson C, Frayling TM, Kritchovsky SB, Spector TD, Richards JB, Lehtimäki T, Ouwehand WH, Kraft P, Cooper C, März W, Power C, Loos RJ, Wang TJ, Järvelin MR, Whittaker JC, Hingorani AD, Hyppönen E. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. PLoS Med 2013;10:e1001383.

78. Jamka M, Woźniewicz M, Jęszka J, Mardas M, Bogdański P, Stelmach-Mardas M. The effect of vitamin D supplementation on insulin and glucose metabolism in overweight and obese individuals: systematic review with meta-analysis. Sci Rep 2015;5:16142.

79. Rejnmark L, Bislev LS, Cashman KD, Eiríksdottir G, Gaksch M, Grübler M, Grimmes G, Gudnason V, Lips P, Pilz S, van Schoor NM, Kiely M, Jorde R. Non-skeletal health effects of vitamin D supplementation: a systematic review on findings from meta-analyses summarizing trial data. PLoS One 2017;12:e0180512.

80. Mirhosseini N, Vatanparast H, Mazidi M, Kimball SM. The effect of improved serum 25-hydroxyvitamin D status on glycemic control in diabetic patients: a meta-analysis. J Clin Endocrinol Metab 2017;102:3097410.

81. Asemi Z, Foroozanfard F, Hashemi T, Rahmani F, Jamilian M, Esmaillzadeh A. Calcium plus vitamin D supplementation affects glucose metabolism and lipid concentrations in overweight and obese vitamin D deficient women with polycystic ovary syndrome. Clin Nutr 2015;34:586-92.