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Vitamin D and Obesity

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Abstract

Objective: The prevalence of overweight and obesity is considered an important public issue in the United States and is increasing among both children and adults. There is evidence of aberrations in the vitamin D-endocrine system in obese subjects. Therefore, we will review the role of vitamin D in the adipose tissue.

Methods: Review Medline database literature and discuss the relationship between vitamin D status and obesity.

Results: It has been noted that vitamin D deficiency and obesity share many of the same risk factors, including both indirect – environmental factors (nutritional, racial, geographic, seasonal, and exposure to air pollution) -- -- and direct - genetic risk factors (vitamin D receptor, polycystic ovary syndrome, cytochrome P_{450}, locus 20q13, vitamin D-binding protein gene polymorphisms, and aP2 gene). Vitamin D is fat-soluble and stored in adipose tissue. The serum concentration of 25-hydroxyvitamin D_3($25OHD_3$) is inversely correlated with body weight. The vitamin D receptor (VDR) is present in adipose tissue and may contribute to the action of vitamin D and its analogs in adipocytes. 1,25-dihydroxy-vitamin D_3 ($1,25OHD_3$) exerts its actions mainly via its high affinity receptor VDR through a complex network of genomic (transcriptional and post-transcriptional) and non-genomic mechanisms.

Conclusion: Vitamin D plays a role in the regulation of adipose tissue. Obese individuals may need higher doses of vitamin D supplementation than do lean individuals to achieve optimal levels of $25OHD_3$.Calcitriol modulates adipokine expression and inhibits anti-inflammatory cytokine expression. Calcitriol definitely has a role in the human adipose tissue because of its active form of vitamin D_3 metabolite, their receptors presented in adipocytes, and itse suppression of PTH levels.

Keywords: Vitamin D; Calcitriol; Obesity; Adipocyte

Abbreviations: DM: Diabetes Mellitus; PTH: Parathyroid Hormone; cAMP: Cyclic Adenosine 3,5'-Monophosphate; 1; $25OHD_3$: 1α,25-hydroxyvitamin D_3; $25OHD_3$: 25-hydroxyvitamin D_3; TNF-α: Tumor Necrosis Factor-alpha; LDL: Low Density Lipoprotein; BMI: Body Mass Index; UVB: Ultraviolet-B; QFM: Quartile of fat mas; VDRKO: VDR knockout mice; HWR: waist-to-hip ratio; SNP: Single Nucleotide Polymorphism; PCOS: Polycystic Ovary Syndrome; CYP: Cytochrome P_{450}; pHPT: Pseudo-Hypoparathyroidism; PTPN1: Protein Tyrosine Phosphatase 1β; CYP27B1: 25-hydroxy-vitamin D_3-1α-hydroxylase; UTR: 3'Unstranslated region; DBP: vitamin D-Binding Protein; ALBP: Adipocyte Lipid Binding Protein; FAS: Fatty Acid Synthase; UCP: Uncoupling Protein; BAT: Brown Adipose; ROS: Reactive Oxygen Species; MSC: Mesenchymal Stem Cells; PPAR: Peroxisome proliferator-Activated Receptor gamma; ER: Endoplasmic Reticulum; SREBP-1C: Sterol Regulatory Element Binding Protein 1c; C/EBPb: CCAAT Enhancer-Binding Protein b; PAI-1: Plasminogen Activator Inhibitor-1; aP2: Adipocyte Protein

Introduction

The prevalence of overweight and obesity is considered an important public issue in the United States and is increasing among both children and adults [1]. Adipose tissue plays a dynamic role in the regulated uptake, storage, and release of lipids. Excessive body weight is a risk factor for cardiovascular disease, type 2 diabetes mellitus (DM), metabolic bone disorders, and especially abnormal vitamin D metabolism. There is evidence of aberrationsin the vitamin D-endocrine system in obese subjects [2], such as increases inserum parathyroid hormone (PTH), urinary cyclic adenosine 3,5'-monophosphate (cAMP), renal tubular reabsorption of calcium, and circulating 1α,25-hydroxyvitamin D_3($1,25OHD_3$), as well as decrease in serum 25-hydroxyvitamin D_3 ($25OHD_3$) levels. In overweight women, bone metabolism is disturbed, and certain markers of bone formation (osteocalcin, carboxyterminal propeptide of type I procollagen, and alkaline phosphatase in the blood) are increased [3]. Weight reduction is accompanied by the regression of secondary hyperparathyroidism andan increase in the level of $25OHD_3$ [4-5]. In obese subjects, cholecalciferol supplementation (3,332 IU/day) does not affect weight loss but significantly improves several cardiovascular risk markers, such as decreases in the levels of PTH, triglycerides, tumor necrosis factor-alpha (TNF-α), and LDL (low density lipoprotein) cholesterol, as well as increases in the levels of $25OHD_3$ and $1,25OHD_3$ [6]. Supplement of ~2,000 IU/day of oral vitamin D for 16 weeks is effective at improving vascular endothelial function in overweight African-American Adults [7]. In children, serum adiponectin levels have been reported to increase in patients with vitamin D-deficiency rickets, and decreased significantly with vitamin D treatment [8]; Adiponectin is synthesized and secreted exclusively by the adipose tissue. Therefore, we will review the role of vitamin D in the adipose tissue.

Relationship between Vitamin D & Obesity

The relationship between vitamin D and obesity has been suggested by several lines of evidence, both direct and indirect.

Indirect factors

Nutritional factors: Calcium or dairy products have been reported to be associated with reduced fat mass or weight [9-10]. In the population of northern Norway, there a significant and positive association was found between calcium intake and body mass index (BMI) in men, and negative and significant associations were found

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between the intake of vitamin D and BMI in both sexes [11]. Hill et al. [12] found a positive, significant relationship between calcium intake and serum $25OHD_3$ levels in postmenopausal Irish women. In the young overweight/obese women, vitamin D status was reported to be modified by two hypocaloric diets. Consumption of a cereal diet that was enriched with vitamin D was associated with a greater weight loss than were green and vegetable diets and led to higher serum $25OHD_3$ levels [13]. Beydoun et al. [14] reported that a higher circulating $25OHD_3$ level was associated with a better quality diet, lower percent body fat, and lower number of metabolic disturbances.

Racial factors: Darker skin pigmentation is inversely associated with $25OHD_3$ levels [15]. Serum $25OHD_3$ levels were significantly lower in Pacific Islanders and Maoris compared to Europeans, after making adjustments for age, sex, and time of the year [16]. Obese African-Americans are at an especially high risk of vitamin D deficiency compared to Caucasian-Americans [17-18]. In American children, vitamin D-deficiency is associated with higher visceral adipose tissue in Caucasians and greater subcutaneous adipose tissue in African-Americans [19].

Seasonal factors: A higher level of ultraviolet-B (UVB) radiation exposure is required to maintain vitamin D sufficiency in the winter when compared to the summer. In a study of healthy African-American and Caucasian-America women, Arunabh et al. [18] demonstrated that seasonal variations in thelevels of $25OHD_3$ were associated with the percentage of total body fat mass. There were significant variations in $25OHD_3$ levels across three seasonal intervals. The highest levels of serum $25OHD_3$ observed from June-September and the lowest levels from February-May in both ethnic groups. The changes in $25OHD_3$ levels across seasons were more pronounced in Caucasian-American women compared to African-American women. Similarly, during the summer, 7.1% of African-American women in the lowest quartile of fat mass (QFM) reached 80 nmol/liter, and only 3.7% of those in the highest QFM achieved this level; however, 73% of Caucasian-American women in the lowest QFM reached 80 nmol/liter, and only 30.7% of those in the highest QFM achieved this level. In other reports, there were also marked seasonal variations in absolute serum $25OHD_3$ levels and the prevalence of vitamin D deficiency in subjects with mild to extreme obesity [20-21]. Similarly, measurements of BMI and waist circumference were higher in the winter than during the summer [22]. In Poland, boys born in October-April were taller (by 2-3 cm), heavier (by 2-3 kg), and fatter than boys born in May-September [23]; November-May is the winter period in Poland. In another study, people in the highest QFM had lower peak serum $25OHD_3$ levels and smaller amounts of seasonal variation in serum $25OHD_3$ levels than did those in the lowest QFM [24].

Geographical factors: There is a strong correlation between UVB radiation exposure and the latitude gradients of disease incidence. It has been observed that every 10 degrees distance from the equator, correspondence to progressive decrease in UVB radiation exposure [25]. Solar UVB is the primary source of vitamin D for most people. Using 2 previously published data sets [26-27], Ashraf et al. [28] demonstrated that the geographical factor varied with the change in $25OHD_3$ levels in obese subjects; the prevalences of vitamin D deficiency among African-American children and adolescents were shown to be 57% and 48.7% in Pennsylvania (latitude 40°N) and Wisconsin (latitude 43°N), respectively.

In response to UV irradiation, the level of unscheduled DNA synthesis is significantly lower in adipocytes as compared to murine 3T3-T proadipocyte cells (stem cells) [29]. Chronic UV irradiation exposure has been reported to cause a disappearance of adipocytes [30].

Air pollution exposure factors: Atmospheric pollution has been suggested to be a cause of reduced vitamin D synthesis in the skin. In Australia, Kinley et al. [31] demonstrated a large difference in vitamin D synthesis between populations in an urban canyon (urbanized environment with tall buildings) and those in a typical suburban area (~2.5 km away from urban areas). Increased atmospheric pollution may be related to haze from industrial and vehicle sources and lead to decrease in absorption of UVB photons, thereby reducing cutaneous vitamin D synthesis [32-33]. Agarwal et al. [34] reported that higher levels of atmospheric pollution were correlated to lower amounts of UVB light reaching ground level. They also showed that children living in areas of high atmospheric pollution were at risk of developing the vitamin D deficiency rickets. In a study of Belgian postmenopausal women who participated in outdoor activities during the summer, urban inhabitants were reported to have an increased prevalence of vitamin D deficiency compared to rural inhabitants [35]. In a cross-sectional study, Hosseinpanah et al. [36] demonstrated that living in a polluted area plays a significant and independent role in vitamin D deficiency. Air pollution has long been known as a major adverse risk factor with serious consequences on human health. Automobile traffic around the home has been identified as a major risk factor for the development of obesity in children [37]. Significant differences in adult obesity prevalence exist between rural and urban settings in the Samoan Archipelago; mean BMI increased from rural to urban Samoan [38]. In another study conducted in China population at Qindao, urban men have more risk factors and higher prevalence of the metabolic syndrome than rural men [39].

Direct effects

Genetic factors: Genetic studies provide an excellent opportunity to link molecular variations with epidemiological data. DNA sequences variations such as polymorphisms exert modest and subtle biological effects. Receptors play a crucial role in the regulation of cellular function, and small changes in their structure can influence intracellular signal transduction pathways.

Calcitriol binds to a nuclear receptor, the vitamin D receptor (VDR), which is associated with specific recognition sequences called vitamin D-responsive elements (VDRE). The commonly occurring linked single nucleotide genetic markers (polymorphisms) at the 3end of the VDR gene are the restriction fragment length polymorphism (RFLPs) of BsmI, ApaI, and Taq I and the exon 2 splice site Fok polymorphism. In the absence of VDR, animals display low fat mass, resistance to high-fat-induced fat accumulation, and reduced plasma lipid levels [40]. VDR knockout mice (VDRKO) also displayed atrophy of adipose tissue surrounding the prostate and mammary glands [41-42]. VDR polymorphisms were reported to play a role in adiposity phenotypes [43]. In Hispanic women, the VDRFokIff genotype is reported to be associated with an increase in the waist-to-hip ratio (WHR), which is indicative of the central deposition of body fat and is more specifically associated with an adverse metabolic profile [44]. In subjects with early-onset type 2 DM, the presence of the TT genotype of the Taq I single nucleotide polymorphism (SNP) or of the bb genotype of the BsmISNP account for a difference of approximately 9 kg of body weight (or 4 kg/m^2 BMI) and an approximate ~30% increase in the prevalence of obesity [45]. Individuals with short poly A repeat (ss) and/or absence of the linked BsmI restriction site on both alleles (BB) exhibit significantly higher body weight and fat mass [46]. VDR and estrogen receptor polymorphisms were demonstrated to be associated with total fat mass in young Chinese men [47]. Moreover, human body weight and BMI have been shown to be associated with a BsmI restriction site polymorphism in the nuclear VDR gene [48]. The BsmI VDR

polymorphism seems to influence BMI because the BB carriers tend to have higher BMI and waist circumferences compared to the bb genotype, while the Fok I VDR polymorphism appears to affect insulin sensitivity and serum HDL (high density lipoprotein) cholesterol levels [49]. In another study, however, the BsmI polymorphism in the VDR gene did not seem to predispose the subjects to obesity or insulin resistance, but the BB genotype was connected to an unfavorable lipid profile [50]. Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies, affecting reproductive-age women, and characterized by hyperandrogenism, chronic an ovulation, and abnormal development of ovarian follicles. Central obesity and insulin resistance are common features found in PCOS patients. In addition, abnormalities in the PTH-vitamin D axis were reported in the PCOS patients. Low 25OHD concentrations are correlated with insulin resistance, metabolic risk factors, and obesity in women with PCOS [51-54]. Serum PTH levels are also higher in PCOS patients than ovulatory women without hyperandrogenemia [54-55]. Vitamin D treatment improved glucose metabolism and menstrual frequency in PCOS women [56-58]. Moreover, precocious pubarche (PP) girls may have higher risk of developing PCOS at later ages; the ApaI of the VDR polymorphism was associated with these PP patients [59]. The Apa I genotype "Aa" appeared to be a marker of decreased PCOS susceptibility, whereas the "aa" genotype was associated with an increased risk for PCOS [60]. VDR ApaI variants are also associated with testosterone levels in PCOS women [61]. These findings suggested a role of vitamin D in the PCOS patients.

The cytochrome P_{450} (CYP) is responsible for the oxidation, peroxidation, and/or reduction of vitamins, steroids, and xenobiotics, as well as the metabolism of drugs. The CYP27B1 (25-hydroxy-vitamin D_3-1α-hydroxylase) enzyme catalyzes the 1α-hydroxylation of the $25OHD_3$ to $1,25OHD_3$, the most active form of vitamin D_3 metabolite. 1α-hydroxylase has been reported to be expressed in adipose tissue and is functional in cultured adipocytes [62]. Interestingly, mice lacking CYP27B1 display a lean phenotype that is similar to hypoleptinemia and hyperphagia [63]. Leptin is an obesity-related gene product that is secreted by adipocytes. Congenital leptin deficiency is associated with severe early-onset obesity in humans [64]. Leptin administration to leptin-deficient obese mice suppressed the mRNA expression and activity of renal CYP27B1 [65], and inhibited renal $1,25OHD_3$, synthesis [66].

A genomic DNA clone for $1,25OHD_3$ 24-hydroxylase has been isolated from a human chromosome 20 library [67]. In a genome-wide association study, a variant at the20q13locus was identified as a risk factor for vitamin D insufficiency [68]. Heterozygous inactivating mutations in the GNAS1 exons (20q13.3) were observed in patients with pseudo-hypoparathyroidism (pHPT) [69]. pHPT is characterized by end-organ resistance to PTH and pHPT patients present with a round face, short stature, brachydactyly, heterotopic ossification, and obesity. In the Québec family study, a genome-wide linkage analysis indicated that 20q13.2can influence plasma levels of adiponectin and C-reactive protein, which are related to the obesity phenotype [70-71]. In another study, a genome scan indicated that one or more genes affecting obesity are located in 20q13 [72]. Single nucleotide polymorphisms in the protein tyrosine phosphatase 1β (PTPN1) gene have been reported to be associated with essential hypertension and obesity in two populations of Japanese and Chinese descents [73]. PTPN1 has been shown to dephosphorylate a kinase that is essential in leptin signaling [74-75]. This gene is also located on same chromosome as 20q13. On a high-fat diet, PTPN1-deficient mice were resistant to weight gain, whereas their wild-type littermates became obese [76]. A variation in the 3'unstranslated region (UTR) of PTPN1 was reported to be associated with insulin resistance in obese individuals [77]. The human promyeloid cell line HL-60 differentiates to either monocytes or granulocytes when treated with calcitriol, which induces tyrosine phosphorylation [78]. In this cell line, calcitriolwas also reported to increase the protein tyrosine phosphatase activity [79].

The vitamin D-binding protein (DBP) gene contains conserved nucleotide sequences that respond to adipocyte and mitotic signals [80]. DBP is essential for vitamin D cellular endocytosis and metabolism [81]; thus, variants of the DBP may affect the amount of active vitamin D in adipocytes and, subsequently, obesity. This prepeptide was reported to be up-regulated in obese rats [82]. The binding and bioavailability of vitamin D metabolites were also altered by mono- and polyunsaturated fatty acids but not by saturated fatty acids [83]. An association has been reported between DBP gene polymorphisms and variations in obesity-related traits in Caucasian nuclear families, especially in female [84].

In obese subjects, adipocyte lipid binding protein (ALBP, the human homologues of the mouse protein aP2) and RNA expression was higher in subcutaneous than with omental adipose tissue [85]. In the lean subjects, however, the expression of ALBP protein was not significantly different between the adipose tissue depots. Adipocytes from $aP2^{-/-}$ mice exhibit diminished lipolysis [86-87] and these mice fail to develop insulin resistance normally associated with the ensuing obesity after feeding with high fat diet [88]. In 3T3-L1 adipocytes, calcitriol is reported to decrease adipose-specific (aP2) gene expression [89].

The relationship between allelic variation in vitamin D metabolism and obesity are summarized in Table 1.

Role of Vitamin D in Obesity

Vitamin D and the adipocyte

Vitamin D is fat-soluble and readily stored in adipose tissue. In 1971, Lumb et al. [90] suggested that vitamin D is sequestered after absorption, stored in tissues such as fat and muscle, and then released slowly into the circulatory system where it becomes biologically available. This fate of vitamin D was demonstrated by injecting radio-labeled vitamin D_3 into individuals and observing the highest levels of biological activity and radioactivity in the fat tissue [91]. Prolonged UV light irradiation of normal rats indicated that adipose tissue, muscle and plasma could hold very large amounts of D_3 [92]. In animal models, the adipose tissue is the major storage site for vitamin D_3 and is a source available for conversion to other metabolites during periods of deprivation [93]. In another study, decreased $25OHD_3$ levels were observed during obesity and may have been secondary to alterations in tissue distribution resulting from increases in adipose mass [94]. The percentage body fat content is independently inversely related to the serum $25OHD_3$ levels in healthy women, regardless of dietary vitamin D intake, season, age, and race [18]. The association between $25OHD_3$ concentrations and adiposity was stronger for visceral than for subcutaneous abdominal adiposity [95]. This relationship was present even among healthy, lean individuals who might otherwise not to be considered at risk for vitamin D deficiency. Vitamin $25OHD_3$ concentrations in subcutaneous fat tissue and serum were inversely and similarly correlated with body weight [96]. The incremental increase in blood $25OHD_3$ concentrations was 57% less in the obese than in the non-obese subjects after exposure to whole-body UVB radiation; however, the percentages for conversions to previtamin D_3 and vitamin D_3 were similar in both groups [97]. Therefore, obese individuals need a higher than normal intake of vitamin D to attain

Linked to	
1. VDR:	
❖	
❖ Absence VDR	Low fat mass, resistance to fat-induced obesity and reduced plasma lipid levels
Atrophy of the adipose tissue surrounding the prostate and mammary glands	
❖ **VDR Polymorphism**	Total fat mass in young Chinese men
• *Taq*I	
TT allele	Increase prevalence of obesity in type 2 DM
• *Fok*IEffect on insulin sensitivity and serum HDL-cholesterol	
ff genotype	Increase in waist-to-hip ratio
Adverse metabolic profile	
bb genotype	Increased prevalence of obesity in type 2 DM
*Bsm*I	Human body weight and BMI
	No predisposition to obesity and insulin resistance
BB allele	Higher BMI and waist circumference relative to *bb* allele
Unfavorable lipid profile	
short poly A- repeat (ss)	Higher body weight and fat mass
2. Polycystic Ovary Syndrome: Central obesity and insulin resistance **(PCOS)**	
+ Low 25OHD concentrations	Correlated with insulin resistance, metabolic risk factors, and obesity
+ Serum PTH levels	Higher in PCOS patients than ovulatory women without hyperandrogenemia
+ Vitamin D treatment	Improved glucose metabolism and menstrual frequency
+ ApaI genotype "Aa" of VDR	Appeared to be a marker of decreased PCOS susceptibility.
+ApaI genotype"aa" of VDR	Associated with an increased risk for PCOS
+ VDR ApaI variants Associated with testosterone levels in PCOS women.	
3. Cytochrome P_{450}:	
• ***CYP27B1***	
Converts $25OHD_3$ to $1,25OHD_3$	Express in adipose tissue and function in adipocytes
Lacking *CYP27B1*	Lean phenotype with hypoleptinemiaandhyperphagia
4. Chromosome 20: Clone for $1,25OHD_3$ 24-hydroxylase	
Variant at 20.13	Risk for vitamin D deficiency
Obesity	
PTPN1	Essential hypertension, obesity (Japaneseand Chinese)
Mutation at 20q13.3	Pseudohypoparathyroidismand obesity
Variant at 20q13.2	Influence plasma levels of adiponectinand C-protein
5. Vitamin D-binding protein (DBP):	
DBP gene	Contains conserved nucleotide sequences that respond to adipocyticand mitotic signals
	For vitamin D cellular endocytosis and metabolism
DBP gene variant	Obesity-related trait in Caucasian nuclear families

VDR, vitamin D receptor; DM, diabetes mellitus; HDL, high density lipoprotein; $25OHD_3$, 25-hydroxyvitamin D_3; $1,25OHD_3$, 1,25-dihydroxyvitamin D_3; PTPN1, protein tyrosine phosphatase 1β

Table 1: The relationship between allelic variations in vitamin D and obesity.

optimal $25OHD_3$ levels compared to lean individuals. Overweight/obese women, however, are at a higher risk of vitamin D deficiency, largely due to excessive adiposity rather than inadequate in take [98]. Vitamin D insufficiency has also been reported to be associated with increased fat infiltration into the muscle in healthy women [99].

Vitamin D deficiency, secondary hyperparathyroidism, and subsequent bone loss are common in patients who have undergone a bariatric surgical procedure for morbid obesity and are due to a combination of baseline deficiency and postoperative malabsorption despite excess weight loss and oral vitamin D supplement [100-103]. However, some studies suggested that high dose of vitamin D supplement, either 5,000 IU/day or 50,000 IU of vitamin D weekly, may correct vitamin D depletion, attenuate cortical bone loss, and improve resolution of hypertension in most patients [104-106].

Role of vitamin D

Obesity has been identified as an important risk factor for heart disease and stroke. The intracellular calcium concentration ($[Ca^{2+}]_i$) plays a key role in metabolic disorders associated with obesity [107]. Increasing $[Ca^{2+}]_i$ via stimulation of either receptor-mediated or voltage-dependent calcium channels stimulates both the expression and activity of fatty acid synthase (FAS), a key enzyme in de novo lipogenesis and inhibits basal and agonist-stimulated lipolysis in both human and murine adipocytes [108-111]. In animal models and in cultures of human adipocytes, calcitriol causes an acute increase in the $[Ca^{2+}]_i$ via activation of calpain and caspase-12 [111-112]. The increased $[Ca^{2+}]_i$ in the adipocytes leads to an activation of lipogenesis and an inhibition of lipolysis via a rapid non-genomic effect. Decreasing the dietary calcium intake could increase body weight by inhibiting lipolysis and increasing lipogenesis through an increase in serum $1,25OHD_3$ [113]. Calcitriol exerts an inhibitory effect on basal as well as isoproterenol and fatty acid-stimulated uncoupling protein (UCP) 2 expression via a genomic effect [113-114].The membrane VDR agonist and antagonist fail to exert their actions to either mimic or prevent the $1,25OHD_3$ inhibition of UCP2 expression, whereas nuclear VDRKO by antisense oligo-deoxynucleotide prevented the inhibitory effect of $1,25OHD_3$. UCP 2 expression is correlated with the basal metabolic rate

in obese women [115]. Over expressing UCP2 in 3T3-L1 preadipocyte cells induced marked reductions in mitochondrial potential and ATP production, increases in the expression of caspases, and decreases in the Bcl-2/Bax expression ratio [116]. Bcl-2 and Bax are apoptotic proteins; the ratio of protective Bcl-2 to apoptotic Bax is widely used to determine the susceptibility to apoptosis through the regulation of mitochondrial function following an apoptotic stimulus. The activation of caspases then induces apoptosis. Physiological doses of $1,25OHD_3$ (0.1-10 nM) restored the mitochondrial potential and protected against UCP2 over expression-induced apoptosis, whereas high dose of $1,25OHD_3$ (100nM) stimulated caspase-1 and caspase-3 expression and inhibited the Bcl-2/Bax ratio, which was a complete reversal of the effect of lower doses of $1,25OHD_3$ on apoptosis [117]. UCP1, which is a highly specific marker for brown adipocytes and mediates the dissociation of cellular respiration from energy production, was elevated more than 25-fold in VDRKO white adipocyte tissue. This elevated UCP1 coincided with a resistance to high-fat diet-induced weigh gain in VDRKO mice [63]. This study identified a novel role of VDR on lipid accumulation and gene expression in adipose tissue. Brown adipose tissue (BAT) is thought to have a protective role against obesity because the genetic ablation of BAT leads to obesity in mice [118]. Classically, adult humans have been considered not to possess active BAT. Zingaretti et al. [119], however, demonstrated that human adults indeed possess BAT with the presence of UCP1. Calcitriol also reported directly to down regulate UCP1 and UCP3 expression in BAT [120]. The production of reactive oxygen species (ROS) has been shown to be increased in obesity [121]. Calcitriol has been demonstrated to stimulate $[Ca^{2+}]_i$, inhibit UCP2 expression, stimulate reactive oxygen species (ROS) production and cell proliferation in adipocytes [122]. In porcine mesenchymal stem cells (MSC), calcitriol stimulates adipocytic differentiation and increases the concentrations of mRNA encoding peroxisome proliferator-activated receptor gamma (PPARɤ), lipoprotein lipase, and adipocyte-binding protein 2 [123]. In the MSC of the senescence-accelerated mice (SAM-P/6), however, calcitriol inhibits bone marrow adipogenesis by decreasing the expression of PPARɤ2 and thus contributes to their differentiation into osteoblasts to form new bone [124]. Calcitriol and its analogs were reported to inhibit the adipogenesis and PPARɤ2 gene transcription in the murine 3T3-L1preadipocyte cell line [125-126]. This cell line offers an ideal model system to understand adipocyte development. In rat hepatoma (H4IIE) cell lines, nuclear VDR represses the transcriptional activity of PPARα (but not PPARɤ) in a $1,25OHD_3$-dependent manner [127]. PPARα potentiates fatty acid catabolism in the liver and is activated by the lipid-lowering fibrates, whereas PPARɤ is essential for adipocyte differentiation. In mice, calcitriol was also demonstrated to inhibit bone marrow adipogenesis. Lee et al. [128] suggested that calcitriol-mediated induction of the endoplasmic reticulum (ER) protein insulin-induced gene 2 (Insig-2) in 3T3-L1 adipocytes might lead to the inhibition of adipogenesis by preventing a transcription factor, sterol regulatory element binding protein 1c (SREBP-1C), from reaching the nucleus. Insig-1 and Insig-2 have been shown to restrict lipogenesis in mature adipocytes and block differentiation of preadipocytes [129]. Recently, Blumberg et al. [130] have further defined the molecular mechanism by which unligandedVDR and calcitriol-ligandedVDR regulate adipogenesis. In the presence of calcitriol, VDR blocks adipogenesis by down-regulating both CCAAT/enhancer-binding Protein b (C/EBPb) mRNA expression and C/EBPb nuclear protein levels at a critical stage of differentiation. In the absence of calcitriol, unliganded VDR appears necessary for lipid accumulation because knockdown of VDR expression using siRNA both delays and prevents this process. Kawada et al. [131] proposed that the active form of vitamin D acted as a suppressor on adipocyte development via ligand-dependent transcriptional regulators.

The UVB has been reported to decrease all PPAR subsets (α, β, and γ) at the mRNA level [132]. The UVA inhibits adipogenic differentiation of human adipose tissue-derived mesenchymal cells and its action mechanisms [133]. The mRNA levels of PPAR γ target genes [lipoprotein lipase, CD36, adipocyte protein (aP2), and C/EBPα] were reduced by the UVA. Application of calcitriolon the dorsal skin prior to UV irradiation dramatically prevented both the disappearance of adipocytes and the accumulation of extracellular matrix components in the lower dermis [134].

Plasminogen activator inhibitor-1 (PAI-1) is known as a risk marker for coronary artery disease. High PAI-1 activity is a frequent finding in obesity. In obese subjects, subcutaneous adipose tissue secreted greater amounts of PAI-1 and had a higher PAI-1 gene expression than visceral adipose tissue [135]. In human coronary artery smooth muscle cells (SMC), calcitriol and its analogs down regulated the expression of PAI-1 mRNA and protein in a dose-dependent manner [136].

Conclusion

In humans, there are limited numbers of studies on the effect of vitamin D on obesity [6, 137-139]. Their results, however, indicated that there was no effect on weight change and that there was slight improvement in cardiovascular risks with cholecalciferol. Obese individuals may need higher than usual doses of vitamin D_3 supplementation to attain optimal $25OHD_3$ compared to lean individuals. Cholecalciferol supplement, however, has no effect on cytokines and markers of inflammation in obese subjects [140]. Calcitriol, inversely, modulates adipokine expression and inhibits anti-inflammatory cytokine expression [141]. Calcitriol definitely has a role in the human adipose tissue because of its active form of vitamin D_3 metabolite, their receptors presented in adipocytes and its suppression of PTH levels. PTH excess observed in elderly subjects with both primary and secondary hyperparathyroidism may promote weight gain [142].

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