DERLEME REVIEW

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1,25-Dihydroxycholecalciferol: Effects on Metabolic Syndrome and Obesity: Traditional Review

1,25-Dihidroksikolekalsiferol: Metabolik Sendrom ve Obezite Üzerindeki Etkiler: Geleneksel Derleme

Hatice Tuğçe BERBEROĞLU[a], Aysun HACIŞEVKİ[b]

[a]Department of Nutrition and Dietetics, KTO Karatay University School of Health Sciences, Konya, TURKEY
[b]Department of Biochemistry, Gazi University Faculty of Pharmacy, Ankara, TURKEY

ABSTRACT Metabolic syndrome (MetS) is a medical term used for a combination of abdominal obesity, dyslipidemia, impaired glucose homeostasis and hypertension, of which its prevalence is increasing in the world. Insulin resistance (IR) and abdominal obesity are considered to be the main reasons for metabolic syndrome development. It is also thought that 1,25 dihydroxy cholecalciferol (vitamin D, calcitriol) deficiency generates a risk of metabolic syndrome development. Maintaining a balanced calcium and phosphorus level is the main function of vitamin D. Vitamin D also affects the cardiovascular system, immune system, intestines, brain and pancreas. Vitamin D metabolizing enzymes and vitamin D receptors exist in some cell groups including diverse immune cells such as B cells, T cells, monocytes and antigen presenting cells. Vitamin D deficiency occurs as a consequence of obesity and it is also a risk factor for the development of obesity. The mechanisms underlying the association between obesity and vitamin D deficiency is not fully understood however, the sequestration theory is the most accepted theory that may explain why obese individuals have lower serum 25-hydroxyvitamin D (calcidiol) levels. In addition, calcitriol deficiency may result in adipogenesis by increasing lipogenesis, inducing catecholamine levels and enhancing parathyroid hormone levels. In this review, the relationship between vitamin D deficiency, MetS, obesity and IR is to be reviewed. In addition, possible underlying mechanisms between these disorders and vitamin D deficiency will be examined.

Keywords: Metabolic syndrome; obesity; insulin resistance; vitamin D deficiency; calcitriol

ÖZET Metabolik sendrom (MetS), abdominal obezite, dislipidemi, bozulmuş glukoz homeostazı, hipertansiyon kombinasyonu için kullanılan tıbbi bir terimdir ve dünyada yaygınlığı artmaktadır. İnsülin direnci (IR) ve abdominal obezite, metabolik sendrom gelişiminin ana nedenleri olarak kabul edilmektedir. 1,25 dihidroksi kolekalsiferol (D vitamini, kalsitriol) eksikliğinin de metabolik sendrom gelişme riskine katkıda bulunduğu düşünülmektedir. Kalsiyum ve fosfor seviyesini dengeli bir şekilde korumak, D vitamininin temel işlevidir. D vitamini ayrıca kardiyovasküler sistemi, bağışıklık sistemini, bağırsakları, beyni ve pankreası etkilemektedir. D vitamini metabolize eden enzimler ve vitamin D reseptörleri, B hücreleri, T hücreleri, monositler ve antijen sunan hücreler gibi çeşitli bağışıklık hücreleri dâhil olmak üzere bazı hücre gruplarında bulunmaktadır. D vitamini eksikliği obezitenin bir sonucu olarak ortaya çıktığı gibi obezite gelişimi için de bir risk faktörüdür. Obezite ile D vitamini eksikliği arasındaki ilişkinin altında yatan mekanizmalar tam olarak anlaşılamamıştır. Bununla birlikte, sekestrasyon teorisi, obez bireylerin neden daha düşük serum 25-hidroksivitamin D (kalsidiol) seviyelerine sahip olduğunu açıklayabilecek en çok kabul gören teoridir. Ek olarak kalsitriol eksikliği, lipogenezi artırarak, katekolamin seviyelerini indükleyerek ve paratiroid hormon seviyelerini yükselterek adipogeneze neden olabilir. Bu derlemede; D vitamini eksikliği ile MetS, obezite ve IR arasındaki ilişki gözden geçirilecektir. Ek olarak bu bozukluklar ile D vitamini eksikliği arasındaki olası altta yatan mekanizmalar incelenecektir.

Anahtar Kelimeler: Metabolik sendrom; obezite; insülin direnci; D vitamini eksikliği; kalsitriol

Vitamin D is an important prohormone and it has an important role in maintaining calcium and phosphorus homeostasis levels, modulation of immune functions, bone mineralization, controlling of cell proliferation and differentiation.[1] Vitamin D is not only supplied with dietary foods and supplements, but also produced in human skin by sunlight exposure.[2,3] The two major forms are vitamin D_2 or ergocalciferol and vitamin D_3 or cholecalciferol. Vitamin D_3 is produced in the human skin and oily fish and

Correspondence: Aysun HACIŞEVKİ
Department of Biochemistry, Gazi University Faculty of Pharmacy, Ankara, TURKEY/TÜRKİYE
E-mail: abozkir@gazi.edu.tr

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cod liver oil are the main dietary sources of vitamin D_3, while vitamin D_2 is produced from ergosterol, which exists in mushrooms and yeast.[3] Exposure of skin to ultraviolet-B radiation transforms the 7-dehydrocholesterol to previtamin D_3 (Figure 1). Previtamin D_3, produced from skin and diet, is then transferred in the blood to Vitamin D binding protein (DBP) and to the liver. In the liver, previtamin D_3 is metabolized to 25-hydroxyvitamin D, also known as calcidiol, through P450 vitamin D 25-hydroxylase. Then calcidiol is hydroxylated to 1,25-dihydroxyvitamin D, which is its active form by 1α-hydroxylase in the kidney.[4]

While there is no agreement about the optimum level of serum calcidiol, it is suggested that serum 25(OH)D levels of <50 nmol/L (<20 ng/mL), 50-80 nmol/L (20-32 ng/mL), 135-225 nmol/L (54-90 ng/mL), >250 nmol/L (>100 ng/mL) and >325 nmol/L (>150 ng/mL) are classified as deficiency, insufficiency, normal, excess and intoxication, respectively.[5] Vitamin D deficiency affects nearly half of the population all around the world. Obesity, dark skin, decreased sun exposure, age, usage of sun cream, decreased absorption of vitamin D, and a vegetarian diet are the main risk factors behind this widespread deficiency. Heritable disorders and limited skin synthesis of vitamin D are also among the triggering factor of vitamin D deficiency.[6] People who have fat malabsorption or have undergone gastric bypass operation are also at risk.[7] The major reasons for vitamin D deficiency are given in Table 1.[5,6]

Vitamin D has a pivotal role in especially calcium and phosphate metabolism and it maintains skeletal health.[3,6] Vitamin D also affects bones, immune and cardiovascular systems, pancreas, intestines and brain health.[6] Vitamin D deficiency has been emerging as a public health issue in worldwide and it is related to autoimmune diseases, cancer, neurocognitive disorders, infections and cardiovascular diseases according to epidemiological studies.[2,8] Vitamin D deficiency causes some other chronic illnesses like obesity and MetS.[9,10] Additionally obesity may also induce vitamin D deficiency development.[11]

Insulin normally reduces blood glucose level via causing glucose uptake in insulin responsive tissues such as adipose, skeletal muscle and heart. Additionally, insulin prevents glucose release in the kidney, liver and small intestine. In case of insulin resistance (IR), insulin induced glucose uptake to insulin sensitive tissues is impaired. Inflammation, mitochondrial dysfunction, hyperinsulinemia, genetic disposition, lipotoxicity, endoplasmic reticulum stress, fatty liver, obesity, hypoxia are thought to be important risk factors for IR development.[12,13] The most accepted reason for the etiopathogenesis of MetS is IR.[14] Vitamin

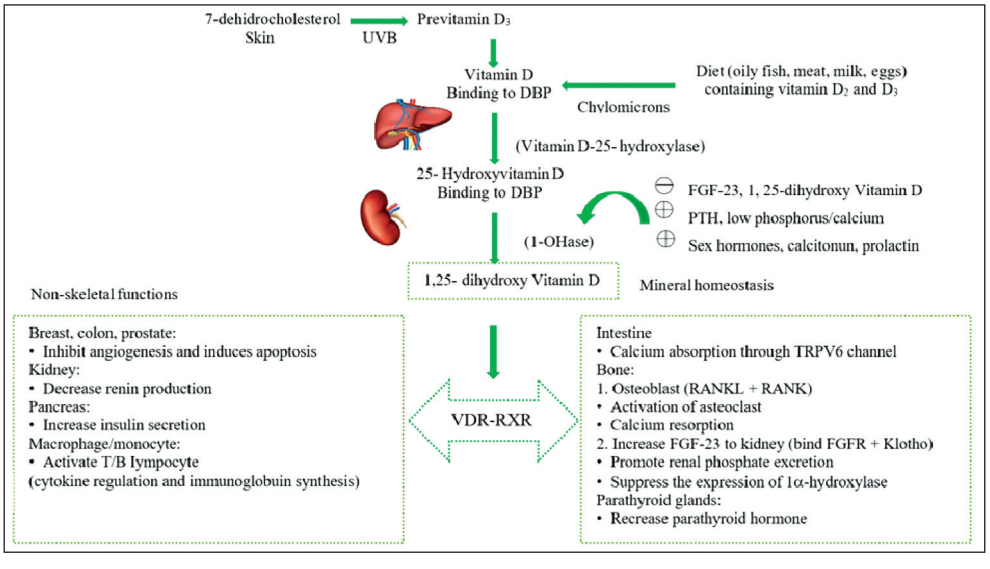

FIGURE 1: Functions of calcitriol.[4]

DBP: D binding protein; UV-B: Ultraviolet-B; PTH: Parathyroid hormone; VDR: Vitamin D receptors; RXR: Retinoid receptor.

TABLE 1: Vitamin D deficiency.[5,6]

Cause	Example
Decreased skin synthesis	Aging, use of sunscreen, pigmentation
Reduced bioavailability	Malabsorption diseases such as celiac disease, cystic fibrosis, Crohn's disease, Whipple's disease and medication usage that decrease cholesterol absorption
Increased catabolism	Anticonvulsant, glucocorticoid usage
Increased sequestration	Obesity
Breastfeeding	Human milk contains poor vitamin D
Reduced synthesis of 1,25-dihydroxyvitamin D	Chronic kidney disease
Reduced synthesis of calcidiol	Hepatic failure
High urinary calcidiol loss	Nephrotic syndrome
Inherited disorders	Vitamin D resistance

D affects glucose homeostasis by maintaining beta cell function or peripheral insulin sensitivity with several mechanisms.[4]

MetS is a rising public health issue of this century and it is a clustering risk factors like high blood pressure, impaired fasting blood glucose, central obesity, triglycerides and reduced high-density lipoprotein cholesterol (HDL-C) level.[14] Central obesity and IR are thought to be two major factors for MetS development. In addition, genetic disposition, advanced age, physical inactivity and pro-inflammatory state may also contribute to MetS development.[15] An another triggering factor for MetS development is vitamin D deficiency.[16] Its deficiency disrupts insulin sensitivity and secretion, decreases the parathyroid hormone (PTH) secretion, decreases vasoconstriction, affects cholesterol transport, lipogenesis, induces pro-inflammatory state and thereby leads to MetS development.[4,17,18-21]

Obesity is a complex and multifactorial disease and it causes many lifelong diseases such as cardiovascular diseases, some kinds of cancer, obstructive sleep apnea syndrome, non-alcoholic fatty liver disease, polycystic ovary syndrome and cerebrovascular disease.[22] Obesity is reported to cause the development of Type 2 diabetes mellitus (T2DM), prediabetes, dyslipidemia and hypertension that lead to MetS.[23] It also contributes to various cardiovascular disease risk factors, which are related to IR.[16] Obesity is described as abnormal and excessive fat accumulation and it is expressed by body mass index (BMI). To calculate BMI, body weight (in kilograms) is divided by the square of height (in meters).[24] According to the World Health Organization, an ideal BMI value should be in the 18.5 to 24.9 range.[25] The prevalence of obesity and being overweight in the world has doubled since the 1980s and now one-third of the population worldwide is categorized as obese or overweight.[25] Lifestyle treatments such as healthier dietary pattern, increased physical activity, pharmacotherapy and surgery are suggested for obesity management.[26] Decreased vitamin D level is found to be related to obesity development.[19] In addition, obesity may be a risk factor that leads to vitamin D deficiency.[11,27] In the paper, the main goal is to examine the relationship between the status of vitamin D and metabolic syndrome, obesity and IR, and to review the possible underlying reasons for the link between these metabolic disorders and vitamin D.

THE RELATIONSHIP OF VITAMIN D STATUS WITH METABOLIC DISORDERS

There is some evidence that vitamin D prevents cardiometabolic diseases and cancer development and it has an anti-inflammatory effect as well as affecting the skeleton system. The biosynthesis of the active metabolite calcitriol by peripheral tissues and immune cells has been thought to have immuno-modulatory features that are similar to locally active cytokines.[28] There is a linkage between deficiency of vitamin D and pathogenesis of IR related diseases.[29] Vitamin D deficiency is linked to insulin sensitivity and resistance and T2DM were shown in human and animal models.[30]

VITAMIN D AND IR

Calcitriol has an important effect on glucose homeostasis via preserving beta cell function and maintaining peripheral insulin sensitivity or both.[4] There are some potential mechanisms that may elucidate that vitamin D has an affirmative effect on IR. Vitamin D induces insulin receptor expression by regulating intracellular calcium (Ca^{+2}).[30] Optimal levels of intracellular Ca^{+2} have a pivotal role in insulin action. A changed level of intracellular Ca^{+2} may cause IR. Calcitriol affects insulin sensitivity by regulating the extracellular level and its flux to cell membranes.[31] Vitamin D deficiency causes IR by inducing the increased concentration level of Ca^{+2} and decreased glucose transporter 4 activity in skeletal muscle.[29,31] Another mechanism is that calcitriol leads to increased insulin sensitivity by inhibiting the renin-angiotensin-aldosterone system (RAAS).[32,33] In addition, it has been suggested in human and animal studies that since vitamin D improves mitochondrial function, lipid turnover and substrate oxidation, it has an effect on insulin sensitivity.[34] Vitamin D receptors (VDR) and vitamin D-metabolizing enzymes are expressed in insulin-sensitive tissues.[34] Additionally, vitamin D affects the pancreatic cells and its secretory function via their nuclear VDR.[30] It is reported that vitamin D has an effect on increased insulin sensitivity in adipose tissue, liver, and skeletal muscle via binding of 1,25-dihydroxyvitamin D to VDR result in IRs expression induction and peroxisome proliferator-activated receptor (PPAR)-δ activation.[29,31]

$1,25(OH)_2D$ binds to VDR first, in turn, this complex binds to retinoid receptor (RXR). The formed $1,25(OH)_2D$-VDR-RXR complex binds to vitamin D responsive elements in the promoter of the insulin receptor gene. Eventually, the IR gene that plays a significant role in the insulin signaling pathway, is activated. Subsequently, calcitriol induces IR expression and maintains insulin sensitivity in human and animal models.[29,31] Since calcitriol has an antioxidative property, it has been suggested that calcitriol prevents oxidative stress-induced impairment. Thus, calcitriol maintains a normal insulin signaling pathway.[35]

Another possible mechanism of the relationship between calcitriol deficiency and IR is adiponectin level. Adiponectin has an insulin-sensitizing effect in peripheral tissues and modulates gluconeogenesis. The mechanism between vitamin D and adiponectin level has not been fully understood, however, adiponectin and vitamin D metabolisms are modulated by osteocalcin.[29] Also calcitriol has an inhibitory effect on some pathophysiologic mechanisms that lead to beta cell dysfunction.[35] Dendritic cells, macrophages, B lymphocytes and T lymphocytes can synthesize calcitriol which protects pancreatic β cells from immune attacks and all these cells can regulate the immune responses.[4] As vitamin D has an anti-inflammatory effect, it has a favorable effect on insulin releasing and it decreases the IR.[36] Vitamin D deficiency activates the nuclear factor kappa B (NF-kB) signaling pathway that causes IR via islet beta cell volume reduction and insulin secretion disorder. Increased NF-kB activity also induces increased secretion of cytokines and chemokines and causes β cell damage.[37] Gene polymorphisms of VDR, DBP or vitamin D 1 alpha hydroxylase (CYP1 alpha) genes may contribute to disturbed insulin releasing and causes IR. Thus polymorphisms linked to vitamin D can be a risk factor for the development of IR.[4]

There are many studies suggesting that vitamin D deficiency is linked to IR (Table 2). Huang et al. have found that vitamin D deficiency is linked to IR in non-diabetic young subjects.[38] In a study conducted by Zaki et al., calcitriol deficiency was remarkably related to elevated homeostatic model assessment for insulin resistance.[30]

VITAMIN D AND METS

It has been suggested that deficiency of calcitriol takes a pivotal role in the improvement and pathogenesis of MetS.[16] The impacts of low calcidiol status on MetS development are shown in Figure 2. There are some potential mechanisms that may explain the effects of vitamin D deficiency on MetS components.[4,17]

Polymorphisms in DBP, VDR or vitamin D 1alpha-hydroxylase genes can cause the changed insulin release. It has been related to impaired insulin secretion and insulin sensitivity.[4,17] Vitamin D also affects insulin sensitivity in adipose tissue and skeletal muscle via modulating extracellular calcium level,

TABLE 2: The relationship between vitamin D and metabolic disorders.

References	Sample Size	Major Findings
8	559 subjects	No significant association between indices of insulin sensitivity and vitamin D level was found. However strong relationship were found between calcidiol level and fasting and 2 hour OGTT
66	65 subjects	Vitamin D supplementation had no effect on insulin secretion and sensitivity
67	71 subjects	OGTT test and glycemic status were not improved with vitamin D supplementation.
68	128 subjects	Cholecalciferol supplementation improved IR markers.
69	3240 subjects	Higher serum 25(OH)D level was associated with lower MetS prevalence.
70	846 subjects	Serum calcidiol levels were not significantly different between individuals with and without MetS.
18	352 subjects	Inverse association between serum calcidiol level and increased risk of hypertension, abdominal obesity and abnormal glucose homeostasis was found. However, there was no significant association between MetS and serum calcidiol level.
71	858 subjects	Vitamin D deficiency was found to related to adiposity.
72	1090 subjects	No association between serum calcidiol level and BMI was found.
61	11 randomized controlled study with 947 subjects.	Vitamin D supplementation may be potential therapeutic option for the body weight loss.
73	2700 subjects	MetS was more common among individuals with vitamin D level deficient compared to individuals with have normal level of serum calcidiol.
58	13 studies	Optimal concentration is unknown for obese individuals and there was no clear evidence for vitamin D supplementation in obese subjects.
17	463 subjects	Calcitriol deficiency was associated with increased risk of MetS development in postmenopausal women.
74	50 subjects	Calcitriol supplementation improved dyslipidemia.
75	125 subjects	Improved blood glucose and cholesterol profile was found with vitamin D supplementation.
59	21 subjects	Increased BMI and decreased vitamin D level is related. Calcitriol has affirmative effect on excess adiposity. Additionally interventions to prevents adiposity may help to increase calcidiol level.

OGTT: Oral glucose tolerance test; BMI: Body mass index; MetS: Metabolic syndrome.

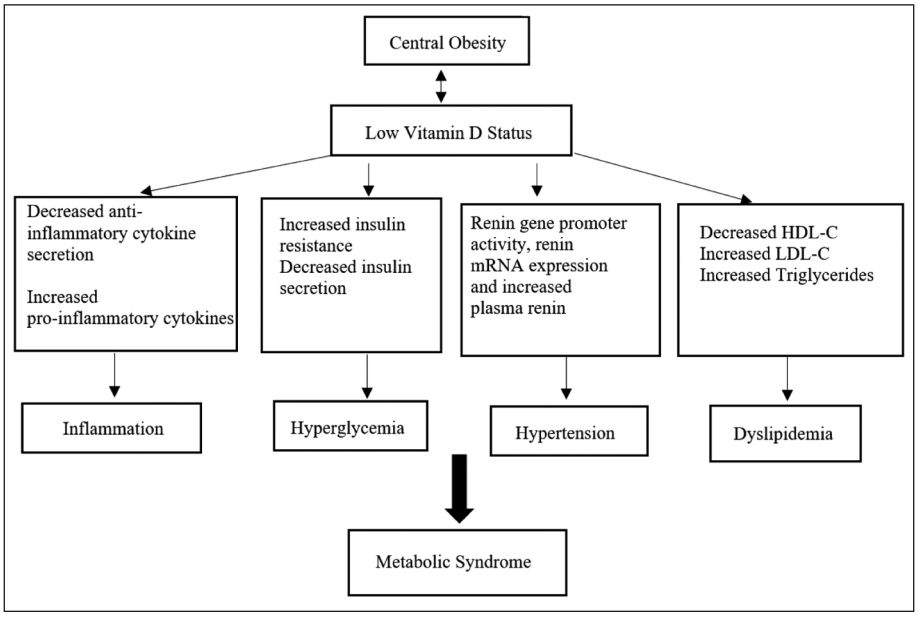

FIGURE 2: The mechanism of obesity-linked MetS development.
HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.

which is necessary for insulin mediated intracellular processes.[17] Furthermore, energy expenditure may be attributed to the relationship between MetS and vitamin D.[39] The potential mechanisms of low calcidiol levels associated with hypertension may be explained with vitamin D suppresses RAAS and inhibits PTH excretion. It has also been suggested that VDRs are found in vascular endothelial cells, vascular smooth muscle and cardiac muscle cells and there is an inverse relationship between vitamin D and hypertension.[18] Even though the exact mechanisms are not fully understood, calcitriol is associated with higher HDL-C level. It has been suggested that vitamin D deficiency may be a risk factor for pathologic lipid profile and lead to coronary artery disease. In addition to affecting the formation of HDL-C, vitamin D may contribute to lowering cholesterol levels by affecting the pathway that synthesizes cholesterol from bile acids.[17] The association between MetS, vitamin D levels and the effect of the vitamin D deficiency on the underlying mechanism of MetS development are needed to be clarified with large scale prospective studies.[8] In a meta-analysis, it has been revealed that elevated vitamin D level is associated with a 51% reduced risk of MetS development.[40] More studies evaluated the relationship between MetS and vitamin D level are shown in Table 2. In these studies, inconsistent results may be explained by different ages, gender, ethnicity, diet, skin pigmentation, study design, sample size, methods for evaluating serum calcidiol concentrations.[8,18]

VITAMIN D AND METS'S COMPONENTS

Vitamin D and Hypertension

Vitamin D has a crucial role in down-regulating the RAAS. It leads to decreased angiotensin II levels and induces vasoconstriction. It also reduces renin release by modulating endothelial vasodilation and calcium flow.[20] Chen et al. found that vitamin D supplementation has been shown to reduce renin, aldosterone and angiotensin levels and blood pressure.[41] In addition, it has an anti-inflammatory effect and reduces oxidative stress leading to decreased blood pressure.[18-20] Moreover, vitamin D decreases blood pressure by suppressing PTH secretion.[18,42,43] The PTH receptor is found in vascular endothelial tissue and smooth muscle cells, suggesting that PTH may have effects on the vessel wall. In addition, calcitriol has a modulatory effect of inflammatory cytokines on vascular tissue, which expresses 1α-hydroxylase.[42] There is a reverse association between blood pressure and serum calcidiol levels.[18-20,44] Ahmad et al. have found lower vitamin D status in hypertensive patients compared to the control group.[45] In two meta-analysis, vitamin D_3 supplementation at a daily dose of >800 IU and ≥800 IU respectively, decreased systolic and diastolic blood pressure and increased serum 25(OH)D concentrations.[46,47]

Vitamin D and Dyslipidemia

Vitamin D regulates the apolipoprotein A-1 levels and it has an important role in cholesterol transport. It also regulates lipoprotein metabolism and reduces synthesis and secretion of triglycerides in the liver by increasing very low density lipoprotein cholesterol receptor expression, vitamin D regulates plasma lipid levels via reducing oxidative stress and thanks to its anti-inflammatory effect.[20,48] Also vitamin D modulates calcium metabolism by increasing calcium absorption; thereby leads to reduces intestinal fatty acid absorption.[49] Increased calcium level also induces conversion of cholesterol into bile acids in the liver, this causes decreased cholesterol concentration.[50] In addition, vitamin D deficiency results in increased PTH concentrations that increase lipogenesis and so influx calcium into adipocytes. Increased PTH also decreases lipolytic activity which results in higher triglycerides level.[48] An inverse relationship has been found between serum calcidiol levels and hypertriglyceridemia in 841 individuals.[51] Lower calcidiol level was associated with dyslipidemia in Indian subjects.[52] Decreased vitamin D level was linked to decreased HDL-C and increased triglyceride levels.[8,53] There are results that a low serum calcidiol level is associated with unfavorable lipid profile in pediatric obese people, non-obese children and adolescents.[48,54] More results associated with the relationship between dyslipidemia and vitamin D level are demonstrated in Table 2.

Vitamin D and Blood Glucose Level

The mechanism between vitamin D deficiency and hyperglycemia is not understood exactly but it has

been attributed to the anti-inflammatory property of calcitriol, which affects insulin sensitivity positively.[8] The affirmative effect of vitamin D on glucose homeostasis is probably because of the effect of vitamin D on insulin effect. Vitamin D receptor is expressed in pancreatic beta cells, and it is a reason for the calcitriol and has a beneficial effect on insulin secretion and beta cell function.[18] Calcidiol levels were reversely related to fasting blood glucose among adolescents.[8,55] There was a reverse connection between vitamin D level and risk of diabetes, MetS and IR, suggesting that adequate this vitamin level may help to prevent metabolic diseases in a meta-analysis.[56] In Mansouri et al.'s study, it has been reported that there was an inverse relationship between calcidiol levels and glucose homeostasis.[18] Inconsistent with other studies, no association between serum calcidiol and fasting glucose level was found.[38] The fact that studies were not long enough, large enough or do not include the appropriate subject population, may explain the inconsistent results.[8]

Vitamin D and Waist Circumference

There is a bidirectional relationship between adiposity and calcidiol level. Even though the association between the mechanism underlying the interaction between adiposity and serum vitamin D level is not fully known, increased sequestration or the volume dilution theory in obese individuals is the most accepted mechanism. This increased adiposity causes increased sequestration of calcitriol, suggesting decreased serum calcidiol levels in obese individuals. As adiposity increased, calcitriol is retained by the adipose tissue and this reduces vitamin D bioavailability, causing increased hunger and decreased energy expenditure. Decreased serum vitamin D level results in lipogenesis via hyperparathyroidism.[21] Tamer et al. found that as the serum calcidiol level decreases, waist circumference increases.[57] There are also more consistent results were demonstrated in Table 2.

VITAMIN D AND OBESITY

Obesity is known as a risk factor for cardiovascular disease development and there is an association between calcitriol deficiency and obesity.[19] Calcitriol deficiency is prevalent in obese individuals.[58] There is a bidirectional connection between vitamin D and obesity, suggesting that vitamin D deficiency is connected with an increased risk of obesity; also, obesity causes vitamin D deficiency.[11,27,59] There are some possible mechanisms that explain decreased vitamin D levels in obese subjects. Obese individuals are tended to be less exposed to sunlight exposure and have less outdoor activity.[60,61] These are the main reasons for vitamin D deficiency in obese individuals. Additionally, adverse dietary habits and decreased supplementation consumption affect serum vitamin D levels negatively.[58] However dietary vitamin D intake has little effect on serum calcidiol level. Thus, the effect of vitamin D consumption with diet on serum vitamin D levels in obese individuals is considered to be the less probable mechanism.[60] Changes of some enzymatic pathways such as a decrease in hepatic 25-hydroxylation in liver and degradation of the calcidiol related vitamin D metabolism in obese individuals also leads to calcitriol deficiency.[58] Additionally, changed vitamin D metabolism in adipose tissue is associated with downregulation of vitamin D-metabolizing enzymes.[34] It has been found that gene expression in calcitriol metabolizing enzymes between obese and normal weight was different. The difference in gene expression between normal weight persons and obese persons also explains the cause of low serum calcidiol level in obese subjects.[62] The increased generality of calcitriol deficiency among obese individuals is mostly explained by larger body volume and sequestration in adipose tissue.[34,58,60] This sequestration theory is the most accepted underlying mechanism for calcitriol deficiency in obese individuals. Thus, obese individuals are required 2-5 times more vitamin D compared to their healthy counterparts to prevent or treat vitamin D deficiency.[60] Even though volumetric dilution is the most accepted theory, other mechanisms also contribute to calcitriol deficiency.[11]

In some other studies, lower calcidiol level is one of the pathogenesis of obesity, unlike the consequence of obesity and reported some mechanisms related to this.[11] Calcitriol decreases triglyceride accumulation in 3T3-L1 (cell line derived from (mouse) 3T3 cells that is undifferentiated fibroblast-like preadipocytes) preadipocytes and prevents adi-

pogenesis.[29] However, vitamin D deficiency contributes to increased PTH level that induces calcium influx into adipocytes, which increases lipogenesis and causes catecholamine to induce lipolysis.[11] All these contribute to fat accumulation and weight gain. Also, increased PTH level may induce weight gain via sympathetic nervous system-mediated thermogenesis and lipolysis. Calcitriol contributes the apoptosis in adipocytes.[61]

Another statement is that active calcitriol prevents adipogenesis with VDRs.[11] Accordingly, decreased level of vitamin D results in increased differentiation of pre-adipocytes to adipocytes.[11,27] However, as there are limited clinical studies, the definite position of calcitriol deficiency on obesity development is not fully understood.[11] Epidemiological studies reported that as sun exposure is low during winter, declined vitamin D synthesis contributes to increased fat mass. Consequently, obesity is considered to be a result of an excessive adaptive response during the colder times of the year-that is why increased vitamin D levels may increase energy consumption through the separation of oxidative phosphorylation in adipose tissues.[27] Another study showed that an increase in serum calcidiol level was lower among obese individuals compared to people with normal weight after vitamin D supplementation and it has been suggested which vitamin supplementation should be individualized in accordance with body size.[63] Therefore, scientific authorities including the British Obesity and Metabolic Surgery Society, International Osteoporosis Foundation, Endocrine Society, Health Council of the Netherlands, Central Europe Guidelines, Geriatric Society, American Society for Metabolic and Bariatric Surgery, American Society for Metabolic and Bariatric Surgery, Interdisciplinary European Guidelines on Surgery of Severe Obesity and the Scientific Advisory of Nutrition Committee recommend the higher calcidiol level for obese individuals.[58]

Weight loss was shown to lead to increased serum calcidiol level via releasing of calcitriol sequestered in the adipose tissue.[64] It is expected that the calcidiol level is increased after weight loss by bariatric surgery however, Chakhtoura et al. found that following bariatric surgery, even with vitamin D supplementation, serum vitamin D level was <30 ng/mL.[58,65] Changes in the gastrointestinal tract, and thus impaired digestion, malabsorption, changes secretion of incretins may cause vitamin D deficiency after bariatric surgery.[58] In numerous studies, the association between calcitriol deficiency and obesity is confirmed (Table 2). There are a few mechanisms that clarify the underlying association between vitamin D status and obesity. However, the causal relationship is not clear yet, thereby there is a need for further investigations.

CONCLUSION

Calcitriol deficiency is a crucial public health problem in the world. The deficiency of calcitriol is associated with various diseases especially bone diseases, cancer, cardiovascular diseases and T2DM. Numerous studies have revealed a strong relationship between MetS, IR and obesity. There is a bidirectional association between obesity and serum calcidiol levels. Lower dietary intake decreased outdoor activity or less bioavailable forms of vitamin D in increased adipocytes may explain why obese subjects have lower serum calcidiol levels. Additionally, impaired hepatic 25-hydroxylation and gene expression are also other reasons, however, volumetric dilution and sequestration theory are the most accepted underlying mechanisms. Calcitriol deficiency is also a risk factor for the development of obesity by contributing to increased PTH secretion, inducing VDR and decreasing energy expenditure. Even though there are inconsistent results, calcitriol deficiency prevalence is common among individuals with IR. Vitamin D has receptors on pancreatic cells and it is related to IR by affecting insulin sensitivity. As it downregulates the RAAS, it has an anti-inflammatory effect and suppresses PTH secretion, thus it can decrease blood pressure. Vitamin D also regulates blood lipid levels by affecting lipid metabolism due to its anti-inflammatory effect. All these factors may explain the mechanism between calcidiol levels, IR, MetS and obesity.

In conclusion, it is clear that calcitriol has important impacts on MetS, its components, IR and obesity. Epidemiological and clinical studies confirm that calcitriol has an affirmative effect on IR and related

disorders. However, prospective or randomized controlled clinical trials involving large case series are still needed to elucidate the potential mechanisms underlying the association between calcitriol and metabolic disorders to develop new therapeutic approaches.

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Conflict of Interest

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Authorship Contributions

Idea/Concept: *Hatice Tuğçe Berberoğlu, Aysun Hacışevki;* ***Design:*** *Hatice Tuğçe Berberoğlu, Aysun Hacışevki;* ***Control/Supervision:*** *Aysun Hacışevki;* ***Literature Review:*** *Hatice Tuğçe Berberoğlu, Aysun Hacışevki;* ***Writing the Article:*** *Hatice Tuğçe Berberoğlu, Aysun Hacışevki;* ***Critical Review:*** *Aysun Hacışevki.*

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