Chapter

Vitamin D and Obesity

Sabrina Ait Gacem and Moyad Jamal Shahwan

Abstract

Obesity is a very common issue worldwide, and it is one of the risk factors for mortality. Several studies were done to identify the causes of this issue and to investigate factors that can affect this condition. Vitamin D is claimed to have an impact not only for maintaining bone health but also for having an association between its deficiency and obesity as some studies found that the concentrations of this vitamin are low in obese individuals. The suggested mechanisms and a discussion of the latest findings as well as the possibility of integrating supplementation in the treatment of obesity are covered in this book chapter. It was concluded that vitamin D deficiency is prevalent in many parts of the world and the supplements are an affordable option, but further studies are required to address different confounding factors that will result in clear data interpretation and will contribute to the future planning of health policies and guidelines used by healthcare professionals.

Keywords: vitamin D, deficiency, supplements, obesity, health, BMI

1. Introduction

Obesity is one of the most commonly observed health issues and can be defined as the condition in which there is an abnormal or excess fat accumulation in the body that can affect the health of an individual [1].

A measure of the obesity and other body weight status is the body mass index (BMI) which is a tool that uses the weight and the height of an individual. The weight is divided by the square of the height. If the BMI is 30 or more, the individual will be considered obese. BMI provides a measure of obesity and overweight that is general for female and male adults from different age groups, but for children the age has to be taken into consideration. Due to its inconsistent representation and correspondence for the level of fat in various individuals, it should be used as a rough guide [1].

According to the World Health Organization (WHO), obesity is known to be high especially in developed countries (high-income countries), but recently it was observed to increase even in middle- and low-income countries as well which is a serious issue because obesity is one of the main risk factors for several serious chronic diseases that are noncommunicable diseases (NCDs) like respiratory diseases, cardiovascular diseases, diabetes, and cancers causing an estimated 38 million deaths annually according to the WHO statistics [1].

According to the Global Health Observatory (GHO), data from the WHO statistics of the prevalence of obesity among adults aged 18+ (1975–2016) represented 27.8% in the United Kingdom (UK) and 31.7% in the United Arab Emirates (UAE) among adults [1]. According to the National Health Survey, adult obesity in the UAE stands at 27.8% in 2019 [2]. Obesity is caused by several reasons, and one of them is

the imbalance between calories expended and calories consumed due to changes in physical activity and dietary patterns [3].

The prevalence of obesity was found to be due to several factors especially change in lifestyle habits besides the genetic contribution and other factors, and this indicates that certain healthcare awareness activities and certain interventions can help and contribute to overcome this issue [4].

Vitamin D is a very important vitamin and plays a role in the maintenance of bone tissues, the balance of phosphorus and calcium, as well as other cell functions [5].

During sunlight exposure, the skin is penetrated by ultraviolet B photons by which pre-vitamin D3 is isomerized into vitamin D3 by the body heat [6].

Although many controversies still exist suggesting that vitamin D is not connected to any health condition and it is just a marker of general good health, there is also a good evidence of the relation between vitamin D level and malignancies as well as mental health, bone health, and other health issues [7].

Vitamin D has a vital role in maintaining good health, and its benefits or importance comes from its role in absorbing calcium and phosphorus from the gastrointestinal track, which is why it can be used to treat and prevent bone and muscle aches as well as chronic fatigue, teeth and dental problems, and osteoporosis [8].

Vitamin D deficiency contributes to many chronic metabolic and endocrine diseases [9, 10]. Vitamin D deficiency causes rickets and growth retardation and an enhanced risk of adult fractures [11, 12]. Obesity was found to be significantly associated with low calcium serum levels especially abdominal obesity [13, 14].

It is also associated with other conditions such as enhanced risk of common cancers, infectious conditions, cardiovascular diseases, and other diseases [15, 16].

In a recent study of 2018, it was observed that vitamin D supplements only increase bone density in adults with 25-hydroxyvitamin D $\leq$ 30 nmol/L, and the study suggested the implementation or use of supplements [17].

Vitamin D deficiency is connected as well to high myocardial diseases and cardiovascular risk; however, the way it works is yet to be investigated in further details [18]. A recent study held in 2018 showed a significant association between low plasma vitamin D levels and prevalence of hypertension. There was a statistically significant correlation between vitamin D deficiency and acute coronary syndrome [19].

On the other hand, a study found that the supplementation of calcium in addition to vitamin D did not diminish the danger of chronic heart disease or stroke and did not have an effect on the incident of hypertension [20, 21].

Several patients with low vitamin D level remain undetected, with bone chemistry values within the reference ranges, unless clinical suspicion is raised. Clinical suspicion based on history and awareness of risk factors should remain the gold standard for requesting vitamin D measurements [22].

2. Suggested mechanisms of action

The body obtains energy from the ingested food, and part of this energy is utilized to maintain the regular body activities while the other part can be stored in the adipose tissue that is able to sense the body energy state. When the body has excess energy compared to the demand, the adipose tissue starts to store the energy as triglyceride in the lipid droplets [23, 24].

The process of lipolysis in which the triglycerides get broken into free acids is activated by catecholamines by the cAMP signaling pathway which activates the protein kinase A. The hormone-sensitive lipase enzyme (HSL) that promotes

the translocation of lipid droplet which will lead to access to triglyceride stores is phosphorylated by protein kinase A [24, 25].

The activity of the proteins can be changed after being formed through a mechanism called phosphorylation. A phosphate group which is provided by ATP is added to a protein by enzymes referred to as kinases [24].

When the body requires energy, lipolysis occurs. The adipose triglyceride lipase (ATGL) enzyme starts hydrolyzing the triglycerides into diacylglyceride. The diacylglyceride is then broken down into monoglyceride by the enzyme hormone-sensitive lipase (HSL), and then the monoglyceride ester bond is cleaved to release glycerol [24, 26].

The lipid droplets in the fat-storing cells in adipose tissue are coated by a protein called perilipin which acts as a protective coat from the body's natural lipases like hormone-sensitive lipase (HSL) that breaks triglycerides into glycerol and free fatty acids for use in metabolism during lipolysis. Phosphorylation of perilipin is important for the mobilization of fats in adipose tissue which is important for the regulation of lipid storage [27].

Insulin suppresses the enzyme hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) as well because insulin enhances the amount of perilipin around the lipid droplets to prevent their access to triglycerides [24].

Vitamin D deficiency is known to occur due to several reasons and through several mechanisms, and one of the stated reasons is the low sun exposure due to decreased mobility due to obesity [14, 24].

Vitamin D is obtained from different sources taken up by the adipose tissue that was suggested to store this vitamin for conditions when the production is reduced. The levels of adipose tissue are inversely correlated with this vitamin level [28].

Several hypotheses were proposed to correlate obesity with vitamin D deficiency, and few of which are due to low physical activities and other reasons which led to limited sun exposure. There was evidence that vitamin D storage, action, and metabolism influences adiposity, and an observational study had shown that there is an increased risk of deficiency among obese individuals, but detailed explained causes are not clear [29].

The hormonal form of vitamin D is (1,25 dihydroxyvitamin D), and besides its known action in the regulation of calcium level, the vitamin D hormone has many other activities such as the regulation of adipocytes [24].

Another hypothesis suggested that the level of vitamin D stimulation enzyme 1-α-hydroxylase in the adipose cells may explain the greater local use of 25(OH)D.

Medical practitioners measure the level of this metabolite to identify a patient's vitamin D status [30, 31]. 25-Hydroxyvitamin D (25(OH)D) is also known as calcifediol, which is a prehormone produced in the liver by hydroxylation of vitamin D3 (cholecalciferol) by the enzyme cholecalciferol 25-hydroxylase. Vitamin D3 gets converted into calcifediol, and this process takes approximately 7 days; then calcifediol is converted in the kidneys (by the enzyme 25(OH)D-1α-hydroxylase) into calcitriol (1,25-(OH)2D3), a secosteroid hormone that is the active form of vitamin D [32].

Variations in serum 25(OH)D and vitamin D reserves can be directly linked to the amount of subcutaneous body fat according to this hypothesis [10, 33]. However, in a cohort study, it was reported that this theory was not enough to address the relationship between vitamin D deficiency and obesity [10, 33].

The active form of vitamin D (1,25-dihydroxyvitamin D) can affect the free fatty acid mobilization from the adipose tissue [34]. Animal studies found that high doses of vitamin D can lead to elevation in energy expenditure because of uncoupling of oxidative phosphorylation in adipose tissues [35].

It has also been suggested that the weather may contribute as obesity can result from an adaptive winter action and vitamin D obtained from the sun is limited during winter which can play a role in the tendency to elevate fat mass during cold weather [36].

Another theory for the correlation between obesity and vitamin D could be that vitamin D is stored in the adipose tissue, and, hence, perhaps the most likely explanation is that the bigger the storage capacity for this vitamin in obese people, the less the circulating [25(OH)D] concentrations in the blood [37].

Another suggested association was between genetic variants that imitate the impact of modifiable environmental exposure and the outcome of interest [38].

A genetic variant linked with lower 25(OH)D concentrations should be linked with BMI if lower vitamin intake is causally linked to obesity. The genetic associations are considered less subjected to confounding factors and socioeconomic and lifestyle factors as genotypes are invariant [39].

Different researches on vitamin D had been made based on the fact that several human cell types carry vitamin D receptor (VDR) which can contribute to several cell functions and regulation [40].

The role of vitamin D receptor (VDR) in the regulation of body energy in vivo was explained in previous studies, and it was observed that when these receptors were inhibited in some animal studies, several body tissues were affected, which made it difficult to interpret the data and make a clear correlation [24, 41]. Some studies suggested that 1.25(OH)D inhibits adipogenesis through actions modulated by vitamin D-dependent receptors, so the decrease in vitamin D can lead to excessive differentiation of pre-adipocytes to adipocytes [10, 42].

It was observed in some studies that obese participants who were subjected to a dose of ultraviolet (UV-B) radiation showed a small response compared to normal-weight participants [37, 40].

The detailed mechanism explaining how this vitamin might be kept in fat was not clearly mentioned, but although the previous mechanism is not detailed, it suggested that vitamin D is relatively tightly bound in tissue depots and not appropriately released to maintain the serum vitamin amount in the blood [40].

Several different levels of sun exposure are not a likely explanation for the link between adiposity and vitamin D deficiency as observed in some studies. Alternatively, it was suggested that extra fat holds the vitamin D metabolites and that the cholecalciferol is partially sequestered by the fat before being transported to the liver for the first hydroxylation [10, 37].

A study concluded that vitamin D serum levels were observed to be (53%) lower among obese participants. Some studies suggested that vitamin D deficiency can favor higher adiposity by promoting elevated parathyroid hormone levels and more calcium inflow into adipocytes which will increase lipogenesis through which acetyl-CoA is converted to triglyceride for storage in fat and packaged within lipid droplets [10, 43].

Identifying and understanding the mechanism beyond low vitamin D status in obesity has a great importance in deciding on appropriate vitamin D replacement doses for obese individuals [40].

However, further studies are required to clarify further the mechanism and the confounding factors that may interfere with the data interpretation such as physical activity, educational level, diet intake, secondary hyperparathyroidism, and other factors.

3. Vitamin D and obesity findings

Several studies were done to identify the causes of obesity and to investigate factors that can affect this condition. Vitamin D is claimed to have an impact not

only for maintaining bone health but also for having an association between its deficiency and obesity as some studies found that the concentrations of this vitamin are low in obese individuals.

Although many controversies still exist suggesting that vitamin D is not connected to any health condition and it is just a marker of general good health, there is also a good evidence of the relation between vitamin D level and several health conditions [7].

It was observed in many studies including a meta-analysis study that vitamin D concentrations were linked to the decrease in the risk of occurrence of metabolic syndrome, diabetes, and cardiovascular diseases [10, 26].

Several studies have shown a positive correlation such as some observational studies that showed a correlation between vitamin D deficiency and obesity with no clear evidence for the detailed causes [9, 10, 44, 45].

Results of a meta-analysis study showed that the deficiency of this vitamin was linked with obesity regardless of the age of participants, and it was concluded that there was no significant correlation with age and many studies were held to assess the increasing risk of developing metabolic syndrome and other disorders like hypertension, excess weight, and cancer with vitamin D deficiency [9, 10, 46].

A recent meta-analysis study revealed as well no significant correlation with latitude or the development status of the country, so it can be concluded that it was found that the correlation between vitamin D deficiency and obesity is not affected by latitude, country status, or age, but a positive association between body mass index (BMI) and vitamin D deficiency was observed and due to the study designs included, it was difficult to clarify the underlying causes [7, 47].

It was concluded from some studies that investigated the relation between vitamin D status and body mass index that on the basis of a bidirectional genetic approach that reduces confounding, a bigger BMI leads to lower 25(OH)D and decreasing BMI is expected to reduce the prevalence of vitamin D deficiency. When obese and nonobese participants were given 50,000 IU of vitamin D orally or exposed to simulated sunlight, the results showed that the obese participants were able to increase the vitamin blood levels by no more than 50% compared with other participants, and this was explained that it is because the body fat sequesters the fat-soluble vitamin which makes obese individuals at higher risk [48, 49].

Similar results were observed in another study that the observed serum vitamin D3 levels in obese individuals were less than that in normal-weight individuals and blood vitamin D2 concentrations after the intake of 50,000 IU of vitamin D2 are inversely correlated with BMI [37].

Similarly, another study concluded that obesity is linked with a lower bioavailability cutaneous synthesized vitamin D and dietary intake which was explained similarly to be due to the sequestration of vitamin D into the adipose tissue [50].

Similarly, other researches have shown that obese individuals tend to have lower blood concentrations of vitamin D3 and 25(OH)D3 than those with normal weights [51–53]. Several studies including epidemiological studies showed a high prevalence increased BMI and low vitamin D status [33, 54–59].

On the other hand, other researches revealed a weak correlation between vitamin D concentrations, and BMI a negative correlation between anthropometric variables and vitamin D level from different races and age groups [10, 47].

4. Integration of vitamin D in obesity treatment

Obesity is caused by many factors, but despite the genetic contribution, it was observed to occur mainly due to lifestyle habits, which indicates that it can be

modified through some interventions or health awareness campaigns. The WHO has identified physical inactivity and unhealthy diet as one of the risk factors for noncommunicable diseases (NCDs), and it urges all efforts to contribute in reducing them to prevent deaths from NCDs [45].

Identifying and understanding the mechanism beyond low vitamin D status in obesity has a great importance in deciding the needed and required vitamin D replacement doses for obese individuals [40].

A study discussed the possibility of integrating vitamin D supplementation with current strategies, and it was suggested that the induction of adipocyte death through apoptosis is a very promising strategy to manage obesity [60–62].

When the adipocytes reach a maximum size, elevation in adipose tissue mass includes as well an elevation in adipocyte number. So, weight loss can result from not only a decrease in adipocyte size but also adipocyte number and can result in the loss of adipose tissue mass. The removal of adipocytes by a process called apoptosis decreases body fat and can contribute to the long-lasting control of weight loss [60–62]. The effects of the hormonal form of vitamin D, 1,25(OH)2D3, on apoptotic cell death are mediated through several signaling pathways on cellular calcium Ca^{2+} [60–62].

High calcium and vitamin D3 intake is linked to the stimulation of the calcium-dependent apoptotic proteases in adipose tissue. The 1,25(OH)2D3-induced cellular calcium signal acts as an apoptotic initiator that directly recruits calcium-dependent apoptotic effectors that are able of causing apoptosis in adipose tissue. It was observed that 1,25(OH)2D3 induces a prolonged elevation in intracellular calcium concentration (the apoptotic Ca^{2+} signal) and is also associated with low lipid accumulation in mature adipocytes [63].

Some studies revealed that vitamin D deficiency was closely associated with enhanced risk of major adverse cardiovascular diseases (CVD) [64, 65]. Some trials revealed a tendency toward a decrease in CVD risk with vitamin D supplementation as well, but the correlation was not significant [66]. Observational studies have indicated that high 25-hydroxyvitamin D [25(OH)D] levels were associated with a favorable serum lipid profile [67]. However, a solid rationale for such association is hard to identify unless there is an effect of vitamin D supplementation on serum lipids in placebo-controlled randomized trials. Unfortunately, the intervention studies gave different results ranging from positive to negative effect [67].

However, some randomized controlled trials (RCTs) studying the effect of supplementation on weight loss in overweight or obese people showed inconsistent results [68].

5. Conclusions

As long as vitamin D deficiency is prevalent in many parts of the world and the supplements are an affordable option, the deficiency of vitamin D may be a common and easily treatable risk factor for several health issues including obesity, but further studies are required to address different confounding factors and variabilities especially prospective studies to study the causal relationship between the deficiency of this vitamin and obesity as well as focus on the safety as well as the required dose regimen. Strong well-structured studies with limited confounding factors that will result in clear data interpretation will contribute to the future planning of health policies and guidelines used by healthcare professionals.

Conflict of interest

The authors declare no conflict of interest.

Author details

Sabrina Ait Gacem* and Moyad Jamal Shahwan
College of Pharmacy and Health Sciences, Ajman University, Ajman,
United Arab Emirates

*Address all correspondence to: sabrinaaitgacem@yahoo.com;
s.aitgacem@ajman.ac.ae

References

[1] WHO. Obesity [Internet]. 2019. Available from: https://www.who.int/topics/obesity/en/ [Accessed: September 04, 2019]

[2] Suchitra Bajpai Chaudhary S. UAE: Nearly 70 Per Cent Emirati Male Adults under 30 'Are Obese' [Internet]. 2019. Available from: https://gulfnews.com/uae/health/uae-nearly-70-per-cent-emirati-male-adults-under-30-are-obese-1.65102616 [Accessed: September 10, 2019]

[3] WHO. Obesity and Overweight [Internet]. 2019. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight [Accessed: September 17, 2019]

[4] Vimaleswaran KS, Loos RJ. Progress in the genetics of common obesity and type 2 diabetes. Expert Reviews in Molecular Medicine. 2010;**12**:7. DOI: 10.1017/S1462399410001389

[5] Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: A systematic review and meta-analysis. Lancet. 2014;**383**:146-155. DOI: 10.1016/S0140-6736(13)61647-5

[6] Wacker M, Holick MF. Sunlight and vitamin D. Dermatoendocrinol. 2013;**5**:51-108. DOI: 10.4161/derm.24494

[7] Al-shahwan M, Gacem S, Shamseddin S, Sammour M. Vitamin D impact on human health and its relation with several diseases. International Journal of Applied Pharmaceutics. 2018;**10**(6):60. DOI: 10.22159/ijap.2018v10i6.28776

[8] Tiwari P, Sharma N. Role of vitamin D in various illnesses. Journal of Pharmaceutical Care & Health Systems. 2017;**4**:3

[9] Afzal S, Brøndum-Jacobsen P, Bojesen SE, Nordestgaard BG. Vitamin D concentration, obesity, and risk of diabetes: A Mendelian randomisation study. The Lancet Diabetes and Endocrinology. 2014;**2**:298-306. DOI: 10.1016/S2213-8587(13)70200-6

[10] Pereira-Santos M, Costa P, Assis A, Santos C, Santos D. Obesity and vitamin D deficiency: A systematic review and meta-analysis. Obesity Reviews. 2015;**16**(4):341-349. DOI: 10.1111/obr.12239

[11] Zaidi S. Power of vitamin d. Endocrine Practice. 2012;**16**:3-99

[12] Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. The American Journal of Cardiology. 2010;**106**:963-968. DOI: 10.1016/j.amjcard.2010.05.027

[13] Shahwan M, Jairoun A, Khattab M. Association of serum calcium level with body mass index among type 2 diabetes patients in Palestine. Obesity Medicine. 2019;**15**:100110. DOI: 10.1016/j.obmed.2019.100110

[14] Shahwan MJ, Khattab MH, Jairoun AA. Association of serum calcium level with waist circumference and other biochemical health-care predictors among patients with type 2 diabetes. Journal of Pharmacy & Bioallied Sciences. 2019;**11**:292-298. DOI: 10.4103/jpbs.JPBS_137_19

[15] Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, et al. Circulating levels of 25Hydroxy-Vitamin D and risk of cardiovascular disease: A meta-analysis of prospective studies. Circulation. Cardiovascular Quality and Outcomes. 2012;**5**:819-829. DOI: 10.1161/CIRCOUTCOMES.112.967604

[16] Barry M, Giovannucci E, Devries E, Møller H. Vitamin D and cancer. The International Agency for Research on Cancer. 2008;**5**:4-303

[17] Macdonald H, Reid I, Gamble G, Fraser W, Tang J, Wood A. 25-Hydroxyvitamin D threshold for the effects of vitamin D supplements on bone density: Secondary analysis of a randomized controlled trial. Journal of Bone and Mineral Research. 2018;**33**:1464-1469. DOI: 10.1002/jbmr.3442

[18] Grober U, Spitz J, Reichrath J, Kisters K, Holick MF. Vitamin D: Rickets prophylaxis to general preventive healthcare. Dermatoendocrinol. 2013;**5**:331-347. DOI: 10.4161/derm.26738

[19] Hallak A, Malhis M, Abajy M. Vitamin-D deficiency and risk of acute coronary syndrome. International Journal of Pharmacy and Pharmaceutical Sciences. 2018;**10**:171. DOI: 10.22159/ijpps.2018v10i6.26469

[20] Hsia J, Heiss G, Ren H. Calcium and vitamin D supplementation and cardiovascular events. Circulation. 2007;**115**:846-854. DOI: 10.1161/CIRCULATIONAHA.106.673491

[21] Margolis KL, Ray RM, VanHorn L. Effect of calcium and vitamin D supplementation on blood pressure: The women's health initiative randomized trial. Hypertension. 2008;**52**:847-855. DOI: 10.1161/HYPERTENSIONAHA.108.114991

[22] Shahwan M, Shahwan M, Abduelkarem A, Ajlouni K, Hyasat D. Prevalence and risk factors of Vitamin D deficiency among type 2 diabetics and non diabetic female patients in Jordan. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2019;**4**(3):278-292

[23] Bezaire V, Mairal A, Ribet C, Lefort C, Girousse A, Jocken J, et al. Contribution of adipose triglyceride lipase and hormone-sensitive lipase to lipolysis in hMADS adipocytes. The Journal of Biological Chemistry. 2009;**284**:18282-18291. DOI: 10.1074/jbc.M109.008631

[24] Wong K, Kong J, Zhang W, Szeto F, Ye H, Deb D, et al. Targeted expression of human vitamin D receptor in adipocytes decreases energy expenditure and induces obesity in mice. Journal of Biological Chemistry. 2011;**286**(39):33804-33810. DOI: 10.1074/jbc.M111.257568

[25] Clifford GM, Londos C, Kraemer FB, Vernon RG, Yeaman SJ. Translocation of hormone-sensitive lipase and perilipin upon lipolytic stimulation of rat adipocytes. The Journal of Biological Chemistry. 2000;**275**:5011-5015. DOI: 10.1074/jbc.275.7.5011

[26] Schweiger M, Schreiber R, Haemmerle G, Lass A, Fledelius C, Jacobsen P, et al. Triglyceride lipase and hormone-sensitive lipase are the major enzymes in adipose tissue triacylglycerol catabolism. The Journal of Biological Chemistry. 2006;**281**:40236-40241. DOI: 10.1074/jbc.M608048200

[27] Greenberg AS, Egan JJ, Wek SA, Garty NB, Blanchette-Mackie EJ, Londos C. Perilipin, a major hormonally regulated adipocyte-specific phosphoprotein associated with the periphery of lipid storage droplets. The Journal of Biological Chemistry. 1991;**266**(17):11341-11346

[28] Bell NH, Shaw S, Turner RT. Evidence that 1,25-dihydroxyvitamin D3 inhibits the hepatic production of 25-hydroxyvitamin D in man. The Journal of Clinical Investigation. 1984;**74**:1540-1544. DOI: 10.1172/JCI111568

[29] Blum M, Dolnikowski G, Seyoum E, Harris SS, Booth SL, Peterson J, et al. Vitamin D (3) in fat tissue. Endocrine.

2008;**33**:90-94. DOI: 10.1007/s12020-008-9051-4

[30] Heaney RP. Functional indices of vitamin D status and ramifications of vitamin D deficiency. The American Journal of Clinical Nutrition. 2004;**80**(6):1706S-1709S. DOI: 10.1093/ajcn/80.6.1706S

[31] Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: Umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ. 2014;**348**:2035. DOI: 10.1136/bmj.g2035

[32] Heaney RP, Armas LA, Shary JR, Bell NH, Binkley N, Hollis BW. 25-Hydroxylation of vitamin D3: Relation to circulating vitamin D3 under various input conditions. The American Journal of Clinical Nutrition. 2008;**87**(6):1738-1742. DOI: 10.1093/ajcn/87.6.1738

[33] Cheng S, Massaro JM, Fox CS, et al. Adiposity, cardiometabolic risk, and vitamin D status: The Framingham Heart Study. Diabetes. 2010;**59**:242-248. DOI: 10.2337/db09-1011

[34] Shi H, Norman AW, Okamura WH, Sen A, Zemel MB. 1alpha,25 Dihydroxyvitamin D3 modulates human adipocyte metabolism via nongenomic action. The FASEB Journal. 2001;**15**:2751-2753. DOI: 10.1096/fj.01-0584fje

[35] Fassina G, Maragno I, Dorigo P, Contessa AR. Effect of vitamin D2 on hormone-stimulated lipolysis in vitro. European Journal of Pharmacology. 1969;**5**:286-290. DOI: 10.1016/0014-2999(69)90150-2

[36] Soares MJ, Murhadi LL, Kurpad AV, Chan She Ping-Delfos WL, Piers LS. Mechanistic roles for calcium and vitamin D in the regulation of body weight. Obesity Reviews. 2012;**13**:592-605. DOI: 10.1111/j.1467-789X.2012.00986.x

[37] Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. The American Journal of Clinical Nutrition. 2000;**72**:690-693. DOI: 10.1093/ajcn/72.3.690

[38] Davey SG, Ebrahim S. Mendelian randomization: Can genetic epidemiology contribute to understanding environmental determinants of disease. International Journal of Epidemiology. 2003;**32**:1-22. DOI: 10.1093/ije/dyg070

[39] Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: Using genes as instruments for making causal inferences in epidemiology. Statistics in Medicine. 2008;**27**:1133-1163. DOI: 10.1002/sim.3235

[40] Drincic A, Armas L, Van Diest E, Heaney R. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. Obesity. 2012;**20**(7):1444-1448. DOI: 10.1038/oby.2011.404

[41] Narvaez CJ, Matthews D, Broun E, Chan M, Welsh J. Endocrinology. 2009;**150**:651-661. DOI: 10.1210/en.2008-1118

[42] Martini LA, Wood RJ. Vitamin D status and the metabolic syndrome. Nutrition Reviews. 2006;**64**:479-486. DOI: 10.1111/j.1753-4887.2006.tb00180.x

[43] Wood RJ. Vitamin D. and adipogenesis: New molecular insights. Nutrition Reviews. 2008;**66**:40-46. DOI: 10.1111/j.1753-4887.2007.00004.x

[44] Earthman CP, Beckman LM, Masodkar K, Sibley SD. The link between obesity and low circulating 25-hydroxyvitamin D concentrations:

Considerations and implications. International Journal of Obesity. 2012;**36**:387-396. DOI: 10.1038/ijo.2011.119

[45] Vimaleswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S. Causal relationship between obesity and vitamin D status: Bi-directional Mendelian randomization analysis of multiple cohorts. PLoS Medicine. 2013;**10**(2):e1001383. DOI: 10.1371/journal.pmed.1001383

[46] Holick MF. Resurrection of vitamin D deficiency and rickets. The Journal of Clinical Investigation. 2006;**116**:2062-2072. DOI: 10.1172/JCI29449

[47] Saneei P, Salehi-Abargouei A, Esmaillzadeh A. Serum 25-hydroxy vitamin D levels in relation to body mass index: A systematic review and meta-analysis. Obesity Reviews. 2013;**14**:393-404. DOI: 10.1111/obr.12016

[48] Buckley R, Holick M. Guideline update: Evaluation, treatment, and prevention of vitamin D deficiency. MD Conference Express. 2011;**11**(5):18-19. DOI: 10.1177/155989771105013

[49] Zhou C, Assem M, Tay JC, Watkins PB, Blumberg B, Schuetz EG, et al. Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. The Journal of Clinical Investigation. 2006;**116**:1703-1712. DOI: 10.1172/JCI27793

[50] Holick MF. Vitamin D deficiency. The New England Journal of Medicine. 2007;**357**:266-281. DOI: 10.1056/NEJMra070553

[51] Tsiaras W, Weinstock M. Factors influencing vitamin D status. Acta Dermato-Venereologica. 2011;**91**(2):115-124. DOI: 10.2340/00015555-0980

[52] Liel Y, Ulmer E, Shary J, Hollis BW, Bell NH. Low circulating vitamin D in obesity. Calcified Tissue International. 1988;**43**:199-201. DOI: 10.1007/BF02555135

[53] Hyldstrup L, Andersen T, McNair P, Breum L, Transbol I. Bone metabolism in obesity: Changes related to severe overweight and dietary weight reduction. Acta Endocrinologica. 1993;**129**:393-398. DOI: 10.1530/acta.0.1290393

[54] Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Archives of Internal Medicine. 2008;**168**:1629-1637. DOI: 10.1001/archinte.168.15.1629

[55] Lenders CM, Feldman HA, Von Scheven E. Relation of body fat indexes to vitamin D status and deficiency among obese adolescents. The American Journal of Clinical Nutrition. 2009;**90**:459-467. DOI: 10.3945/ajcn.2008.27275

[56] Moschonis G, Tanagra S, Koutsikas K. Association between serum 25-hydroxyvitamin D levels and body composition in postmenopausal women: The postmenopausal health study. Menopause. 2009;**16**:701-707. DOI: 10.1097/gme.0b013e318199d5d5

[57] Looker AC. Body fat and vitamin D status in black versus white women. The Journal of Clinical Endocrinology and Metabolism. 2005;**90**:635-640. DOI: 10.1210/jc.2004-1765

[58] Kimmons JE, Blanck HM, Tohill BC, Zhang J, Khan LK. Associations between body mass index and the prevalence of low micronutrient levels among US adults. MedGenMed. 2006;**8**:59

[59] Muscogiuri G, Sorice GP, Prioletta A. 25-Hydroxyvitamin D concentration correlates with insulin-sensitivity and BMI in obesity. Obesity. 2010;**18**:1906-1910. DOI: 10.1038/oby.2010.11

[60] Christakos S, Hewison M, Gardner D, Wagner C, Sergeev I, Rutten E. Vitamin D: Beyond bone. Annals of the New York Academy of Sciences. 2013;**1287**(1):45-58. DOI: 10.1111/nyas.12129

[61] Sergeev IN. Novel mediators of vitamin D signaling in cancer and obesity. Immunology, Endocrine & Metabolic Agents in Medicinal Chemistry. 2009;**9**:153-158. DOI: 10.2174/187152209789760521

[62] Song Q, Sergeev IN. Calcium and vitamin D in obesity. Nutrition Research Reviews. 2012;**25**:130-141. DOI: 10.1017/S0954422412000029

[63] Sergeev IN. 1,25-Dihydroxyvitamin D3 induces Ca^{2+}-mediated apoptosis in adipocytes via activation of calpain and caspase-12. Biochemical and Biophysical Research Communications. 2009;**384**:18-24. DOI: 10.1016/j.bbrc.2009.04.078

[64] Parker J, Hashmi O, Dutton D. Levels of vitamin D and cardiometabolic disorders: Systematic review and meta-analysis. Maturitas. 2010;**65**:225-236. DOI: 10.1016/j.maturitas.2009.12.013

[65] Wang H, Xia N, Yang Y, Peng D. Influence of vitamin D supplementation on plasma lipid profiles: A meta-analysis of randomized controlled trials. Lipids in Health and Disease. 2012;**11**(1):42. DOI: 10.1186/1476-511X-11-42

[66] Wang L, Manson JE, Song Y, Sesso HD. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. Annals of Internal Medicine. 2010;**152**(5):315-323

[67] Jorde R, Grimnes G. Vitamin D and metabolic health with special reference to the effect of vitamin D on serum lipids. Progress in Lipid Research. 2011;**50**(4):303-312. DOI: 10.1016/j.plipres.2011.05.001

[68] Salehpour A, Shidfar F, Hosseinpanah F, Vafa M, Razaghi M, et al. Vitamin D3 and the risk of CVD in overweight and obese women: A randomized controlled trial. The British Journal of Nutrition. 2012;**108**(10):1866-1873