Vitamin D: A Regulator of Metabolism and Inflammation

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Abstract: Vitamin D, a calcitropic hormone, is gaining attention for many aspects of health, particularly metabolic regulation. As societal trends towards increasing caloric intake become more prominent, the concern for diseases stemming from chronic inflammation grows. Excess caloric intake results in increased lipid and fatty acid storage in adipose tissue leading to adipocyte hypertrophy and hyperplasia. Adipocytes produce cytokines and adipose-related hormones and can promote a systematic chronic proinflammatory state with the development of the metabolic syndrome and increasing risk of cardiovascular disease. Proliferative cytokines can signal immunocytes to injure the pancreas and endothelium. This, in turn can result in a reduction in insulin secretion and increasing insulin resistance. Vitamin D may possess therapeutic potential for metabolism associated diseases, as a result of its role in metabolic regulation and its action on adipocytes and myocytes. Vitamin D inhibits adipocyte maturation and differentiation, and reduces the production of proinflammatory cytokines and adipose-related hormones by adipocytes. The purpose of this review is to elucidate the current literature on the therapeutic potential of vitamin D repletion in the treatment and prevention of metabolic and cardiovascular diseases. Although associations exist between vitamin D insufficiency and obesity, diabetes, hyperlipidemia, cardiovascular and all-cause mortality, there have not been prospective trials that have demonstrated the benefit of vitamin D in alleviating manifestations of disease. Nevertheless, correction of vitamin D insufficiency would be expected to confer many health benefits. A greater understanding of the interaction of vitamin D with not only adipose tissue but other components of the human metabolic regulatory system, such as the hypothalamus, pancreas, and bone, may help tailor interventions including vitamin D supplementations that address cardiovascular disease and obesity.

Keywords: Adipocyte, energy, vitamin D, proinflammatory cytokines.

INTRODUCTION: HISTORY AND EFFECT OF EXCESS ENERGY INTAKE

Synthesis of Vitamin D

Vitamin D is a steroid hormone which has multiple functions, including preserving skeletal integrity, neuromuscular function, immunity, and safeguarding against cardiovascular diseases and cancer [1]. Vitamin D can be acquired through diet or naturally produced through UVB exposure to the skin leading to the conversion of 7-dehydrocholesterol into cholecalciferol. Cholecalciferol has little bioactivity, and the canonical pathway for its activation begins in the liver where an initial hydroxylation creates 25-hydroxycholecalciferol (25-OH vitamin D or calcidiol) and subsequent hydroxylation in the kidney creates the active form of vitamin D: 1,25-dihydroxycholecalciferol (1,25-(OH)2 vitamin D or calcitriol). The latter hydroxylase is also present in many other tissues including the colon, pancreas, brain, and skin [2]. Vitamin D status is typically assessed using serum 25-OH vitamin D concentrations, however therapeutic strategies normally involve supplementation with cholecalciferol, 1,25-(OH)2 vitamin D, or analogues such as paricalcitol and alfacalcidol.

EVOLUTIONARY PERSPECTIVE

Despite the availability of vitamin D from both diet and sunlight, many individuals worldwide have subnormal 25-OH vitamin D concentrations (insufficiency ≤ 75nmol/L; deficiency ≤ 25nmol/L) [3]. An evolutionary perspective may provide insight on potential confounding factors to the vitamin D insufficiency pandemic. As the availability of sunlight and natural production of vitamin D during the course of human evolution, through persistence hunting thousands of years ago [4], gave way to man’s migration to colder climates, it became necessary to cover his skin imposing a barrier to vitamin D production. The new environment also expanded into northern latitudes in which daylight times and sunlight exposure were more varied, further diminishing vitamin D synthesis. The potential for vitamin D deficiency and insufficiency were also significantly increased through industrialization as more time was spent indoors. In addition to the impacts on the availability of natural vitamin D sources, the changes may have increased the prevalence of metabolic diseases as life in regions with lower temperatures, where food is cyclically available, required physiologic adaptation in adipose tissue to generate more body heat in the winters and sustain health with less frequent meals [5].

Now, however, these adaptations may predispose individuals to metabolic diseases. Typical western diets contain increasing amounts of energy as a result of advances in food-
production technology. For most of the modern industrialized world, over consumption has become a greater concern than starvation. While the average caloric intake for a resident of the United States is 3770 calories a day [6], the maximum recommended caloric intake for men is 1000-2400 calories a day and for women is 1000-2000 calories a day, depending upon one’s age, body mass, and activity level [7]. Perhaps, in combination with decreased activity levels compared to prehistoric societies (although the activity levels of such societies cannot be known with certainty) [8], this has led to an epidemic in obesity and the attendant increase in morbidity and mortality from obesity-related disease [9]. The effects of excess caloric intake, possibly augmented by prevalent vitamin D insufficiency, include the components of the “metabolic syndrome”, which affects 34.5% of all Americans and includes obesity, dyslipidemia, hypertension, impaired regulation of blood glucose, and sarcopenia [10].

ADIPOCYTE ENERGY REGULATION AND INFLAMMATION

Surplus dietary energy is generally stored in adipocytes making adipogenesis and adipocyte function attractive targets for strategies to prevent and/or treat obesity and sequelae. An overabundance of energy results in adipocyte hyperplasia and hypertrophy [11]. Receptors on adipocyte precursor cells detect nutrient excess and stimulate gene activation by the target of rapamycin (TOR) gene pathway [12, 13]. The TOR pathway in turn up regulates the expression of peroxisome proliferator-activated receptor-γ (PPARγ), a nuclear receptor that is a transcription factor for genes important to the maturation of adipocytes [12, 13]. PPARγ binds with additional nuclear receptors and transcription factors such as retinoid X receptor (RXR) and CCAAT/enhancer-binding protein (CEBP) to promote adipocyte differentiation [14].

Adipocytes do more than store fat; they influence many systemic effects through the production of cytokines and adipose-related hormones leading to an alteration of the growth and structure of the vasculature and regulation of appetite [15-17]. Adipose tissue directly releases numerous proinflammatory cytokines, including TNFα, IL-6, IL-12, and C-reactive protein (CRP), macrophage-chemoattractant pro-tein-1 (MCP-1), colony stimulating factor (CSF), and nitrous oxide synthetase (NOS). In addition proinflammatory cytok-ines are released by adipose tissue resident macro-phages, leukocytes, and fibroblasts under adipocyte regulation [15, 16]. Local release of these factors recruit immunocytes, such as macrophages, leading to further production of cytokines, augmenting the proinflammatory signals [15]. Adipose tissue also releases angiogenic cytokines, such as vascular endothelial growth factors (VEGF), VEGF-C, VEGF-D, soluble VEGF receptor-2 (sVEGFr2), angiogenin, angio-poietin-2, hepatocyte growth factor (HGF), and anti-angiogenic cytokines, such as endostatin [17].

Additionally, adipose tissue secretes leptin, which typically suppresses appetite, although obesity is typically coupled with leptin resistance [18]. Leptin also causes macrophages to produce the highly inflammatory cytokine tumor necrosis factor (TNF-α) and induces the creation of reactive oxygen species (ROS) in endothelial tissue [15]. Adipocytes also produce the hormone resistin, which stimulates macrophages to release TNF-α, interleukin-12 (IL-12), and IL-6, and also induces insulin resistance [15]. Furthermore, adipocytes secrete another inflammatory hormone, retinal binding protein-4, which also causes insulin resistance [16, 19-21]. These inflammatory cytokines not only promote increased adipogenesis and atherosclerosis but lead to an increased risk of the development of vascular diseases.

VITAMIN D ACTION IN ENERGY REGULATION AND ITS INFLUENCE IN HUMAN DISEASE

The notion of using vitamin D as a therapeutic agent for metabolic diseases is supported by the fact that vitamin D receptors are present on adipocytes. Additionally several studies have investigated the localization of vitamin D receptors and vitamin D-activating enzymes in adipose tissue including one in which rats and humans were given radiolabeled vitamin D followed by measurement of body stores; adipose tissue sequestered greater quantities of cholecalciferol than did other organs and tissues, although adipose tissue does not store more vitamin D in obesity [22, 23]. Human preadipocytes can hydroxylate 25-OH vitamin D to its active form 1,25-(OH)2 vitamin D [24].

Vitamin D regulates the size and location of stores of adipose tissue [25]. It has been theorized that seasonal variation in vitamin D intake in more polar latitudes with colder temperatures acts as a signaling mechanism to help animals store calories for thermogenesis [5]. Although it is unclear whether such mechanisms exist in humans, there is significant support suggesting that vitamin D does play a role in weight regulation. Several epidemiological studies reported inverse relationships between vitamin D and measures of adiposity, including overweight and obese individuals. In the Longitudinal Aging Study Amsterdam (LASA) several adiposity indices including body mass index, sum of skin folds, and waist circumference were inversely associated with serum 25-OH vitamin D concentrations (-0.136, -0.140, and -0.137, respectively, p<0.05 for these indices) in 453 subjects at least 65 years old [26]. Percentage body fat content was inversely correlated (-0.13, p=0.013) with 25-OH vitamin D concentrations in a population of 410 US women ages twenty to eighty [27]. There was an association between prevalence of 25-OH vitamin D insufficiency (<75 nmol/L) and obesity in 316 patients in Spanish obesity clinics [28]. In sixty morbidly obese patients awaiting bariatric surgery, there was a significant inverse correlation between body mass index and 25-OH serum vitamin D concentrations [29]. Several other series comparing obese subjects and matched controls have found significantly lower serum 25-OH vitamin D concentrations in obese individuals [30-33]. Overweight women who successfully lowered their body weight by at least 10% for two years had a corresponding 7.5 nmol/L increase in serum 25-OH vitamin D concentration (p=0.014) [34]. Those who lost less weight did not have a significant increase in 25-OH vitamin D concentration. In a recent genetic analysis using Mendelian randomization of 42,024 subjects, an increased BMI was associated with a reduced 25-OH vitamin concentration [35].

Obese individuals may have lower serum concentrations of vitamin D because the lipid-soluble vitamin is distributed
Vitamin D, Metabolism and Inflammation

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VITAMIN D AND METABOLIC SYNDROME

The effects of vitamin D on metabolism may also be mediated by changes in adipose-regulatory hormone levels. The addition of 1,25-(OH)2 vitamin D to human adipose tissue culture in vitro reduces leptin secretion [60]. Twenty-three vitamin D deficient subjects (serum 25-OH vitamin D < 25 nmol/L) who received 300,000 IU of cholecalciferol through intramuscular injections monthly for three months had lower serum leptin levels and greater brachial artery mediated flow dilation (an indication of improved endothelial function) at the conclusion of treatment than at the onset [61]. The systemic significance of vitamin D on leptin secretion has not been determined.

VITAMIN D AND THE METABOLIC SYNDROME

Investigations have often identified an association between the metabolic syndrome and vitamin D concentrations. Data from 8,421 people who participated in the Third National Health and Nutrition Examination Survey (NHANES III) revealed a correlation between the lowest quintile of serum 25OH-vitamin D level and greater risk of metabolic
syndrome (adjusted OR for highest [> 96 nmol/L] relative to the lowest [< 48.4 nmol/L] was 0.38) [62]. In the 1868 participants of the Canadian Health Measures Survey, there was an inverse relationship between serum 25-OH vitamin D concentration and incidence of metabolic syndrome (OR=0.50 between individuals in the highest quartile of serum 25-OH vitamin D concentration as compared to the lowest quartile) [63]. In the Australian Diabetes, Obesity, and Lifestyle Study of 11,247 individuals, the risk of developing metabolic syndrome over five years was significantly higher in those participants in the two lowest quintiles (<45 nmol/L, and 45-75.5 nmol/L; OR 1.41 [95% CI 1.82-1.95] and 1.74 [95% CI 1.28-2.37] respectively) [64]. However, in 39,876 subjects of the Women’s Health Survey, there was no association between vitamin D status and metabolic syndrome, although there was a positive association between dietary calcium intake and metabolic syndrome. Furthermore in 5559 South Koreans, investigators did not find an association between serum 25-OH vitamin D levels and metabolic syndrome risk [65].

**VITAMIN D AND DIABETES**

Higher serum 25-OH vitamin D concentrations have been associated with a lower risk of developing diabetes. Vitamin D was associated with the incidence of type 2 diabetes in 2656 persons between the ages of 41-71 [66]. In this study, there was a direct relationship between waist circumference and vitamin D concentration. Among the 2,039 participants in the Diabetes Prevention Program, those individuals with the highest tertile of 25-OH vitamin D concentration had a lower risk of developing diabetes than others [67]. In a birth cohort study that followed 10,366 children, those who took 2000 IU daily of vitamin D reduced their relative risk of developing diabetes (odds ratio=0.22, 95% CI 0.05-0.89) [68]. In an investigation of 3155 children who participated in the EURODIAB trial, subjects who had received vitamin D had a lower chance of becoming diabetic (odds ratio=0.67, 95% CI 0.53-0.86) [69].

Inhibition of certain cytokines by vitamin D, such as interferon-γ, interleukin-2, and interleukin-12, may prevent the development of diabetes, although randomized-controlled trials have yet to be performed [70, 71]. 1,25-(OH)₂ vitamin D suppresses the release of these cytokines by T cells and dendritic cells *in vitro* [71, 72]. Furthermore, 1,25-(OH)₂ vitamin D inhibits antigen presentation by dendritic cells *in vitro*, suggesting that vitamin D might reduce autoimmune damage in type 1 diabetes by preventing dendritic cells in the pancreas from presenting antigens [70, 72].

Yet *in vivo* studies have not demonstrated a role for vitamin D supplementation in ameliorating diabetes. Treatment of seventy diabetic children with 25 μg 1,25-(OH)₂ vitamin D every other day for one year did not improve glucose control [73]. In subjects with type 2 diabetes but normal fasting glucose, adding alfacalcidiol (1-OH cholecalciferol) increases insulin release in response to a glucose challenge, however, those with abnormal fasting glucose did not benefit [74, 75]. In addition, a single injection of 300,000 IU ergocalciferol resulted in a higher glycosylated hemoglobin and insulin resistance in three vitamin D insufficient Asian subjects with type 2 diabetes [76]. Thus, prospective studies of vitamin D supplementation in the prevention of diabetes by modifying diabetes risk factors, such as reduction of inflammatory cytokines, are warranted.

Vitamin D, including proteins involved in its metabolic pathway, may have additional roles in the pathogenesis of type 2 diabetes [70, 74]. Vitamin D binding protein (DBP), which acts to transport vitamin D and its metabolites systemically, may have genetically based alterations in structure in certain populations of individuals related to type 2 diabetes. Polymorphisms in genes encoding for DBP are associated with variations in insulin secretion and sensitivity in some ethnic populations, but in other populations no correlation was found between DBP variants and type 2 diabetes [74]. Vitamin D may be important in the synthesis and metabolism of insulin [77-81]. In animal models, vitamin D is necessary for insulin secretion by the pancreas and the regulation of glucose [74]. Rats that are deprived of vitamin D have lowered levels of insulin release, exaggerated response to injected insulin, and reduction in insulin sensitivity [74, 82]. 1,25-(OH)₂ vitamin D stimulates pancreatic islet cells to release insulin-regulatory proteins [74]. Vitamin D binding to calcium channels on the membrane of the β-cell allows calcium synthesis which stimulates endopeptidase production that acts to synthesize insulin formation [74]. An association (*p=0.0011*) existed between 25-OH vitamin D concentration and insulin sensitivity index in 128 healthy young subjects on a hyperglycemic clamp [83]. Vitamin D-deficient individuals (1,25-(OH)₂ vitamin D ≤ 30 pg/ml) exhibited increased insulin release after supplementation with 2000 IU cholecalciferol a day for six months [84]. However, glucagon release was not altered [84, 85]. Diabetic patients who were treated with 1332 cholecalciferol once a day for a month had a 34.3% increase in first-phase insulin secretion [86]. Therefore, vitamin D appears to exert beneficial effects on insulin regulation.

There are several associations between vitamin D and the pathogenesis of diabetes [38]. VDRs are located in the beta cells of the pancreas, and VDR polymorphisms are associated with insulin-dependent diabetes and non-insulin dependent diabetes risk [70, 74, 87-90]. An association was found between the VDR receptor gene initiation codon and type I diabetes risk [88]. A relationship has been described between type 2 diabetes and the Apal, TaqI, FokI, and BsmI VDR polymorphisms [74, 91-94], although not all studies agree on their significance. A systematic review of the literature analyzing this relationship in East Asia found a significant relationship between diabetes for the FokI polymorphism and type 2 diabetes, and for Apal and FokI polymorphisms and type 1 diabetes [94]. Epidemiologic studies have given further evidence to a correlation between vitamin D levels and glucose regulation [95]. A genome-wide association study noted enrichment of VDR binding site intervals associated with type 1 diabetes (and other autoimmune associated genes) [96]. There was a correlation between serum 25-OH vitamin D concentration and fasting serum glucose in 753 postmenopausal women (ages 35-94) in Australia (r=0.15, p<0.001) [95].
VITAMIN D AND Cardiovascular Disease And All-Cause Mortality

A number of large investigations have delineated the relationship between vitamin D and cardiovascular disease [97-100]. In the Framingham Offspring study, an inverse correlation was observed between 25-OH vitamin D serum concentration and one of several endpoints: ischemia, heart failure, stroke or MI [97]. In a retrospective analysis of a cohort of 10,899 individuals, there was a correlation between vitamin D insufficiency (<75 nmol/L 25-OH vitamin D) and risk of diabetes, hypertension, coronary artery disease, cardiomyopathy, cardiovascular mortality, and all-cause mortality [98]. Individuals who consumed vitamin D supplements had a lower chance of death (p<0.0001). When serum 25-OH vitamin D concentrations from forty-four patients residing in an inpatient stroke unit were measured every two months for a year and compared with 96 healthy ambulatory subjects, stroke patients had statistically significantly lower 25-OH vitamin D level (seasonally adjusted Z score of stroke patients -1.4 SD units versus controls, p<0.00001) [99]. One-hundred seventy-nine patients who had a myocardial infarction were matched with age- and sex-matched control subjects in several cohorts whose 25-OH vitamin D concentrations were obtained during different seasons of the year [101]. Subjects whose serum 25-OH vitamin D concentration was ≥ 43 nmol/L had a lower risk of MI than those whose levels was < 25nmol/L (relative risk = 0.30, 95% CI 0.215-0.61) [101]. Concentrations of 25-OH vitamin D were significantly lower in 179 patients admitted to the hospital with an MI (32.0 nmol/L) than controls (35.5 nmol/L) [101]. Comparison of hospitalized patients to ambulatory subjects, however, may subject the results to reverse confounding.

Many additional investigations, including meta-analyses, have concluded that serum 25-OH vitamin D concentrations are inversely associated with overall mortality and cardiovascular disease-related mortality [102]. One was conducted on the relationship between vitamin D and mortality involving 57,311 subjects who received various vitamin D supplements [102]. Subjects who took between 200-10,000 IU daily had a lower relative risk of dying than those who did not (relative risk = 0.93, 95% CI 0.87-0.99) [102]. Mean serum 25-OH vitamin D concentrations were 1.4-5.2 fold higher in the intervention than in the control groups. In a second meta-analysis, which included another twelve studies of 32,142 individuals, a 20 nmol/L higher 25-OH vitamin D level correlated with an 8% decreased mortality [103]. The Mini-Finland Health Survey, which followed a cohort of 6,219 persons of at least thirty years of age who did not have cardiovascular disease, found that subjects in the highest quintile of vitamin 25-OH vitamin D concentrations had a lower relative risk for dying from cardiovascular disease (relative risk = 0.76, 95% CI=0.60-0.95) [104]. Interestingly, the risk was primarily attributed to reduction in cerebrovascular disease death; there was not an association between vitamin D concentration and coronary artery disease death [104]. In pooled results from two large epidemiologic trials in 9,146 persons, a higher 25-OH vitamin D concentration was associated with lower all-cause mortality (odds ratio=0.95, p=0.005), although not specifically with ischemic heart disease and stroke [105]. Another meta-analysis of 65,594 subjects revealed a relative risk of cardiovascular disease of 1.03 for every 25 nmol/L decrement below 60 nmol/L [106]. Among 388 people admitted with chest pain secondary to coronary artery disease, low 25-OH vitamin D serum concentrations predicted an increased risk of cardiac death (HR=0.37 for the highest versus lowest quartile of vitamin D concentration, p=0.004) [107]. In 1259 individuals who were admitted for a myocardial infarction, lower quartiles of serum 25-OH vitamin D concentrations were associated with adverse events (subsequent hospitalization for heart failure and subsequent myocardial infarction, but not death) [108]. In 1801 patients following coronary angiography, those with serum 25-OH vitamin D concentrations of at least 75 nmol/L were less likely to die from all causes (HR=0.25) or cardiovascular disease (HR=0.25) [109]. Among 4418 patients undergoing cardiac surgery, those with serum 25-OH vitamin D concentrations of < 30 nmol/L or 30-40.9 nmol/L were more likely to develop post-operative complications (OR = 2.23 and 1.73 respectively) than those whose serum levels were at least 50 nmol/L [110].

Some of the more recent investigations reveal a complex relationship between vitamin D and cardiovascular disease. As noted above in the study of 9,146 participants, baseline serum 25-OH vitamin D concentrations were associated with all-cause mortality over a mean follow-up of 10 years, but there was no relationship between vitamin D concentration and stroke or ischemic heart disease [105]. In 10,001 statin-treated patients with coronary heart disease, serum 25-OH vitamin D concentrations were not associated with cardiovascular events or mortality over a mean follow-up of 14.4 years [111]. There was no relationship between dietary vitamin D intake and cardiovascular events or mortality in 2338 Scottish participants of a epidemiologic study of cardiovascular disease [112]. A study of records of 1,282,822 subjects from Israel who were at least 45 years old provides a more finely nuanced insight into the association between serum vitamin D concentration and cardiovascular disease. Those whose serum 25-OH vitamin D concentrations were both below 50 nmol/L and above 90 nmol/L had a higher probability of developing acute coronary syndromes than did those with 25-OH vitamin D levels between 50 and 90 nmol/L (HR 1.25 p<0.5 for 25-50 nmol/L and HR 1.13 for >90 nmol/L, both p<0.05) [113].

There is an association between vitamin D concentration and mortality that persists into old age. In the Women’s Health and Aging Surveys I and II, in 714 women living in the community between ages seventy and seventy-nine, those participants whose serum level was in the lowest quintile of 25-OH vitamin D concentrations (<38.2 nmol/L) had a greater chance of dying (hazard ratio 2.45, 95% CI 1.12-5.36) than did those in the highest quintile (> 67.4 nmol/L) [114]. Among 3408 persons over sixty-five who were part of NHANES III, subjects whose serum 25-OH vitamin D concentrations were < 25.0nmol/L had a higher relative risk of mortality over a mean follow-up of 7.3 years than those whose serum was > 100 nmol/L (1.83, 95% CI 1.24-2.94) [115]. The relative risk for cardiovascular disease alone was 2.36 (95% CI 1.17-4.75) [115]. Such observations may be explained in part by apparent relationships between vitamin D concentrations and dyslipidemia [38]. Human macrophages from subjects with diabetes cultured with 1,25-(OH)2 vitamin D take up less cholesterol and are less likely to dif-
ferentiate into foam cells [116]. Several epidemiologic studies have described an association between vitamin D concentrations and lipid levels. Concentrations of 25-OH vitamin D were correlated with fasting serum concentrations of apolipoprotein A-1 although not other lipids in a population of 170 healthy persons in Britain of South Asian origin [117]. In 301 Koreans sixty years or older, 25-OH vitamin D concentrations of less than 50nmol/L were associated with hypertriglyceridemia and insulin resistance [118]. An inverse relationship between triglycerides, VLDL cholesterol, and 25-OH vitamin D levels was also observed in 6784 people between the ages of 30 and 60 [119].

THE USE OF VITAMIN D TO TREAT METABOLIC SYNDROME AND RELATED DISEASES AND FUTURE DIRECTIONS

As we have seen, there are associations between vitamin D insufficiency and manifestations of caloric excess. Recent investigations are starting to delineate the potential utility of vitamin D to treat diseases in prospective trials. Such studies have yielded mixed results on the ability of vitamin D to induce changes in adiposity. In one investigation, 110 young (ages 20-40) and elderly (≥ 64) ingested 600 IU of cholecalciferol or a placebo for 5.5 months. In older but not younger subjects, BMI, waist circumference, and fat-free mass were negatively associated with 25-OH vitamin D concentration [120]. In another trial, 171 overweight adults, aged 28-65, consumed orange juice containing 300 IU of cholecalciferol and 1050 mg calcium or a placebo for four months [121]. Although vitamin D supplementation did not induce total weight loss, the subjects who ingested vitamin D lost 13% of their visceral adipose tissue. Individuals supplemented with vitamin D failed to lose weight or body fat despite increases in mean serum 25-OH vitamin D concentration from 58 to more than 100 nmol/L. In the subjects did not have any better glucose tolerance or lipid profile [122]. In another trial in Norway in which 445 overweight participants (BMI 28-47) ages 21 to 70 took 20,000 IU cholecalciferol bi-weekly, weekly, or consumed a placebo for 12 months, vitamin D supplementation did not improve cardiovascular risk factors [123].

The lack of demonstrated ability of vitamin D thus far in prospective trials to improve parameters of metabolic regulation does not mean the effect of vitamin D on metabolism is unimportant. In 171 vitamin D deficient (< 27.5 nmol/L) subjects ages 35 to 65 who took either 500 IU or 50,000 IU cholecalciferol every three months for one year, significant reductions in serum concentrations of the inflammatory cytokines, MMP9 (68%), CRP (23%) and tissue inhibitor of metalloproteinase-1 (TIMP 1) (38%) occurred [124]. The influence of vitamin D on bone metabolism can be influenced by the initial vitamin D levels of the subjects, dose given to subjects, and potential relationship to co-nutrients, such as vitamin A [125]. This may also be true for other effects of vitamin D, such as metabolic regulation. Future investigations need to control for such possible confounding influences. If the initial levels are too low, for example, a low supplementation level may be inadequate to achieve a measurable effect. Furthermore, given the pathophysiology of cardiovascular disease, chronic rather than acute supple-

mentation of vitamin D earlier, rather than later in the course of the disorder, might be necessary for benefit.

The role of vitamin D as a regulatory agent for energy metabolism is one example of our rapidly evolving view of “whole-organ” human energy regulation [126]. This model is quite complex and beyond the scope of this manuscript, but involves a bidirectional positive reinforcing feedback loop between secretion by the osteoblasts in the bone of osteocalcin (which is subsequently decarboxylated into its active form) and insulin secretion by the pancreas [128-130]. Leptin, produced by adipocytes, induces the CNS to augment sympathetic activity, which reduces concentrations of decarboxylated osteocalcin secreted by the bone [128]. Vitamin D co-cultured with osteoblasts, glucose, and insulin augments osteocalcin release [131]. Further research that increases our understanding of how vitamin D regulates energy metabolism in concert with other hormones should be undertaken in order to more completely elucidate the role of vitamin D in the prevention and treatment of metabolic syndrome and cardiovascular diseases.

CONCLUSION

The optimal vitamin D status needed to alleviate the complications of a chronic proinflammatory state associated with or induced by caloric excess may differ from current recommendations for cholecalciferol supplementation needed in most persons to optimize bone health, prevent fractures and reduce falls. Further prospective investigation of vitamin D supplementation targeted to improve diseases reflecting the complications of chronic inflammation will help establish more definitively the importance of vitamin D in the prevention and treatment of metabolic syndrome and cardiovascular diseases.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

Vitamin D, Metabolism and Inflammation


[80] Need AG, O’Loughlin PD, Horowitz M, Nordin BE. Relationship between fasting serum glucose, age, body mass index and serum 25 hydroxyvitamin D in postmenopausal women. Clin Endocrinol (Oxf) 2005; 62: 738-41.


