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EDITORIAL

Vitamin D and Cardiovascular Disease

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Vitamin D exists in several forms comprising steroid-like fat-soluble molecules (secosteroids).[1,] Cholecalciferol (vitamin D3) is synthesized in the skin in response to solar ultraviolet radiation B producing photochemical cleavage of a cholesterol precursor (7-dehydro-cholesterol).[1-3] Irradiation of ergosterol, a membrane sterol found in the Ergot fungus, produces ergocalciferol (vitamin D2). Dietary sources of vitamin D include fish oils (D3), egg yolk (D3), mushrooms (D2), and fortified cereals and dairy products (D2 or D3). Vitamin D derived from all different sources undergoes two successive hydroxylation steps, first in the liver (25-hydroxyvitamin D / calcidiol) and then the kidney (1, 25-hydroxyvitamin D2 / calcitriol). The former form has a longer half-life than the latter (weeks vs. several hours). The biologic effects of vitamin D result largely from its binding to the vitamin D receptor (VDR), a nuclear steroid hormone found in almost every tissue. Calcitriol (D2), the active compound, appears to have the greatest affinity for the receptor. As the VDR is expressed on cardiac myocytes, one can expect direct actions of vitamin D in the heart. In addition, there is a VDR-mediated suppressive effect of the vitamin D upon the renin-angiotensin-system (RAS).[2]

The prevalence of vitamin D deficiency is estimated around 20–50% in the adult population in developed countries, mostly the result of insufficient cutaneous production due to decreased exposure to sunlight, and to a less degree from low dietary intake.[4] A higher prevalence (74%) has been reported in patients with CVD, particularly in those with coronary heart disease and heart failure.[Kim] The serum level of 25-hydroxyvitamin D best represents overall vitamin D status as this measurement reflects total vitamin D from dietary intake and sunlight exposure, as well as the conversion of vitamin D from adipose stores in the liver.[3] Serum levels of 25-hydroxyvitamin D >30 ng/mL are considered adequate, while levels < 20 ng/mL are diagnostic of vitamin D deficiency.

The endocrine functions of vitamin D in relation to bone metabolism and mineral ion homoeostasis are well known.[3] Vitamin D deficiency results in reduced intestinal absorption of calcium, which stimulates the production of parathyroid hormone with an ensuing accelerated bone de-mineralization to maintain serum calcium concentration, with all these alterations leading to the clinical effects of hypocalcemia. These may rarely result in tetany, but due to gradual and insidious development, more commonly produce local, or diffuse musculo-skeletal aches and pains.

Importantly, more recent epidemiological studies have linked vitamin D deficiency with the pathogenesis of ***cardiovascular disease*** (CVD) and an attendant increase in cardiovascular morbidity and mortality, but data for a

causal relationship are still missing.[1,6,7] Experimental studies have proposed novel actions of vitamin D metabolites on cardiac myocytes, as well as on endothelial and vascular smooth muscle cells. Low levels of 25-hydroxyvitamin D are associated with left ventricular hypertrophy, vascular dysfunction, and activation of the renin–angiotensin system.[2,8,9] However, the cardiovascular benefits of vitamin D supplementation in those without renal disease or hyperparathyroidism have not been demonstrated.[10,11] Thus, important questions remain about the real role of vitamin D deficiency as a cardiovascular risk rather than mere reflection of a classic risk burden.

Nevertheless, the evidence is growing suggesting that vitamin D may play an important role in cardiovascular health status. Vitamin D receptor (VDR) and enzymes for vitamin D metabolism are expressed in both heart and vessels. Many observational studies have suggested that vitamin D deficiency may be associated with CVD and its risk factors. Low vitamin concentrations are an independent risk factor for cardiovascular events, including myocardial infarction, strokes and all-cause, cardiac and sudden deaths.[1, 6, 12, 13] An association of *VDR* gene variants with CAD risk has been suggested in a prospective cohort of type II diabetic patients.[14] Some trials with pure vitamin D supplementation have indicated beneficial effects on cardiovascular risk factors such as arterial hypertension.[15,16]

According with the Nova Scotia Health Survey, [17] among 244 patients with prior cardiovascular disease (ischemic heart disease, peripheral vascular disease, or stroke), marked vitamin D deficiency (levels of <15 ng/mL) was associated with an increased risk of ischemic events over a 10-year follow-up period. A total of 114 ischemic events occurred during the 10-year follow-up. Vitamin D levels of <30 ng/mL were associated with a hazard ratio of 1.33 (p=0.172) for ischemic events compared to levels ≥30 ng/mL, but levels of <15 ng/mL were associated with a hazard ratio of 2.30 (p=0.035) for ischemic events compared to levels ≥30 ng/mL.

In a Danish study, plasma 25-hydroxyvitamin D levels were measured in 10,170 people not receiving vitamin D-fortified food.[2] Over 29 years, 6747 died, 3100 individuals developed ischemic heart disease (IHD), and 1625 suffered an acute myocardial infarction (MI). Increasing risk of IHD, MI, and early death was correlated with decreasing plasma 25-hydroxyvitamin D levels. Multivariate analysis indicated that individuals with plasma 25-hydroxyvitamin D levels at the 1st to 4th percentile compared with individuals with levels at the 50th to 100th percentile, had an adjusted risk increased by 40% for IHD, by 64% for MI, by 57% for early death, (or 81% for combined fatal IHD/MI). In the meta-analyses of 18 and 17 studies, risk of IHD and early death were increased by 39% and 46% for lowest vs highest quartile of 25-hydroxyvitamin D level. The authors concluded that with decreasing levels of vitamin D an increasing risk of IHD, MI, and early death was noted, findings which were corroborated in the meta-analyses.[2]

An analysis of the third National Health and Nutrition Examination Survey (1988–1994) (NHANES III) examined the association between serum 25-hyrdoxyvitamin D levels and 8% prevalence of CVD (angina, myocardial infarction or stroke) in 16,603 men and women aged ≥18 years.[18] Participants with CVD had a greater frequency of 25-hyrdoxyvitamin D deficiency (<20 ng/mL) than those without (29.3% vs. 21.4%; $p < 0.0001$). Multivariate analysis indicated that participants with 25-hyrdoxyvitamin D deficiency had an increased risk of prevalent CVD (odds ratio 1.20; $p = 0.03$).

Mechanisms by which vitamin D deficiency may confer increased cardiovascular risk include the development of electrolyte imbalances, pancreatic β-cell dysfunction, and RAS activation.[19] In addition, disrupted adaptive immune responses with severe vitamin D deficiency result in an inflammatory milieu that promotes vascular dysfunction and insulin resistance. Indeed, most epidemiological studies have reported an inverse relationship between vitamin D status and the prevalence of established cardiovascular risk factors such as age, hypertension, diabetes, and hypertriglyceridemia. Serum 25-OH D levels are also lower in women, in obesity, and in those with decreased physical activity. A recent study of 554 subjects indicated that vitamin D insufficiency was associated with increased arterial stiffness and endothelial dysfunction in the conductance and resistance blood vessels, independent of the presence or absence of traditional risk factors.[20] Furthermore, normalization of vitamin D status in insufficient individuals was associated with improvement in vascular function.

The association between vitamin D deficiency and ***hypertension*** perhaps offers the most convincing evidence for the involvement of vitamin D metabolism in the pathogenesis of cardiovascular disease.[16,21,22] Current evidence indicates that vitamin D deficiency may promote vascular dysfunction and sustained RAS activation.[9,20,23,24] Among other studies, the third National Health and Nutrition Examination (NHANES III) looked at serum 25-OH D in relation to CVD risk factors in over 13 000 US adults. [22] After multivariable adjustment, those with 25-OHD levels in the lowest quartile had a significantly higher prevalence of hypertension compared with those in the highest quartile, and sufficient levels

attenuated the expected age-related increases in blood pressure. In addition to its relation to hypertension (odds ratio-OR, 1.30), vitamin D deficiency was also associated with higher prevalence of diabetes mellitus (OR, 1.98), obesity (OR, 2.29), and high serum triglyceride levels (OR, 1.47) (P<0.001).[22] Furthermore, hypovitaminosis D appears to be highly prevalent in various CVDs, such as coronary artery disease, heart failure, stroke and peripheral arterial disease.[5]

With regards to the association of vitamin D deficiency with ***diabetes*** mellitus, experimental data indicate an effect on insulin synthesis, secretion, and sensitivity by modulating pancreatic RAS activity and regulating calcium ion traffic across β-cells. In addition, vitamin D deficiency may produce abnormal immune responses that precipitate an inflammatory reaction and subsequent insulin resistance. Several studies indicate a higher incidence and prevalence of type I diabetes mellitus with depressed vitamin D status, as well as an association with insulin resistance, obesity, glucose intolerance, and type II diabetes.[25] Other potential consequences of vitamin D deficiency may include an exacerbation of atherogenesis and acceleration of arterial calcification. Experimental studies show that vitamin D deficiency may produce endothelial cell dysfunction, while vitamin D supplementation may improve endothelial function in diabetic patients.[26]

Vitamin D deficiency is also most prevalent in ***heart failure*** patients, culminating to 80-95% [27] and may be ascribed to nutritional deficiency, decreased skin production, reduced intestinal absorption, and hepatorenal disease.[28] Hypovitaminosis D has been linked with poor clinical outcomes with increased morbidity and mortality in this patient population.[29] However, it is not clear which is the pathophysiological mechanism involved. It has been suggested that the renin–angiotensin–aldosterone system and pro-inflammatory cytokines may possibly be involved in mediating a poor outcome via the cardiorenal syndrome. Data with regards to the benefit of vitamin D supplementation in ameliorating this relationship remain scanty.[30] Nevertheless, vitamin D may constitute a new therapeutic target in patients with heart failure. Further studies are needed to better clarify the pathogenetic mechanisms and also to further investigate the role of vitamin D monitoring and supplementation in these patients.

A meta-analysis of 18 randomized controlled trials comprising over 57000 patients indicated that oral supplementation of vitamin D (most daily doses at 400-800 IU) was associated with a 7% reduction of total mortality.[11] The authors postulated that various protective mechanisms of vitamin D might have contributed to this benefit. Among them, its pleiotropic skeletal and extraskeletal effects on calcium homeostasis, bone formation, cellular proliferation and differentiation, immune system, rennin production, endothelial function and vascular protection. They also point to effects mediated through the activation of the vitamin D receptor, such as inhibition of cellular proliferation and activation of cellular differentiation, which could reduce aggressiveness of cancerous processes and expansion of atheromatous lesions.[11] However, another meta-analysis of 51 trials indicated a non-significant 4% reduction of cardiovascular mortality conferred by vitamin D.[7] No effect was observed on myocardial infarction or stroke. There is a concern that the addition of calcium in the supplement regimen may be detrimental, although this remains a controversial issue.[2,31,32]

Finally, whether vitamin D deficiency is directly related to CVD or its effect on most CVD risk factors leads to an increased cardiovascular morbidity and mortality remains a moot point. Nevertheless, in either case, further randomized trials are needed to elucidate whether vitamin D supplementation will ameliorate these adverse effects of vitamin D deficiency and provide cardiovascular protection.[2,10] Such ongoing trials, the VITAL and ViDA trials, will examine, in 20,000 (>60 years) and 5000 patients (50-84 years) respectively, the effects of vitamin D (either 2000 IU daily alone or in combination with omega-3 fatty acids; or 100000 IU monthly, respectively) on developing heart disease, stroke or cancer; or heart or respiratory disease or fractures, respectively.[33] Another trial, whereby patients with CVD will be given either 150,000 IU of vitamin D3 every two months or placebo over one year, will assess the association between rise in calcidiol level and incidence of new cardiovascular events.[2]

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