Vitamin D3 and Omega-3 Fatty Acids: A New Approach for Cardiovascular Prevention

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This Commentary relates to the article by A. Mehdawi et al on pages 251-258.

Life is ten percent what happens to you and ninety percent how you respond to it
–Lou Holtz

Vitamin D deficiency (VDD) and insufficiency (concentration <15 ng/mL and 16–30 ng/mL, respectively) are common public health problems affecting all ages and ethnic groups.[1] Emerging scientific investigations have reported that vitamin D is crucial for the modulation of cardiovascular, immunological, and metabolic processes. In particular, within the spectrum of cardiovascular diseases, epidemiologic studies have found VDD to be associated with an increased risk of congestive heart failure, myocardial infarction, peripheral arterial disease, stroke, and related mortality even after adjustment for traditional risk factors.[1] Furthermore, VDD is as an independent risk factor for atherosclerosis because, indeed, it is associated with traditional risk factors, such as hypertension, obesity, dyslipidemia, and diabetes and regulates atherosclerotic biologic pathways.[1] Vitamin D seems also to have a regulatory influence on platelet aggregation, inflammation state, and thrombogenic activity, which are pivotal factors in the atherosclerotic process.

Observational studies have indicated that there is an association between insufficient vitamin D levels and increased oxidative stress or reduced antioxidant defenses, other risk factors for the development of the atherosclerotic process.[2] The mechanism requires the vitamin D–induced upregulation of genes involved in antioxidant response through vitamin D receptor–mediated genomic pathways with additional activation of nuclear-factor-erythroid 2–related factor 2 (Nrf2).[3] Vitamin D3 also has an indirect impact on mitochondria function; indeed, transcriptomic analyses focused on mitochondrial genes showed that vitamin D3 inhibits the expression of several genes involved in oxidative processes and upregulates genes involved in reactive oxygen species defense by Nrf2.[3] Furthermore, in a study using diabetic rats, vitamin D3 injection resulted in the inhibition of nicotinamide adenine dinucleotide phosphate oxidase synthesis in the aorta.[2]

In vitro studies demonstrated that treatment with vitamin D protected human umbilical vein endothelial cells from H_2O_2, contrasted O_2 generation by mitogen-activated protein kinases pathway, and enhanced synthesis of the antioxidant enzyme gluthatione.[4] It seems that vitamin D3 may have a protective role in atherosclerosis because it can increase the expression of oxidized low-density lipoprotein (Ox-LDL) scavenger receptors, including SR-A, CD36, and LOX-1, in diabetic rats[5] and can improve endothelial function by decreasing ICAM1 and oxLDL in type 2 diabetic patients with hypertension.[6] Vitamin D can also affect endothelial function through the nongenomic pathway by the induction of PDIA3-mediated calcium, cAMP, Akt, and PKC downstream signaling. Moreover, vitamin D3 is able to stimulate endothelial cell proliferation and inhibit apoptosis by increasing

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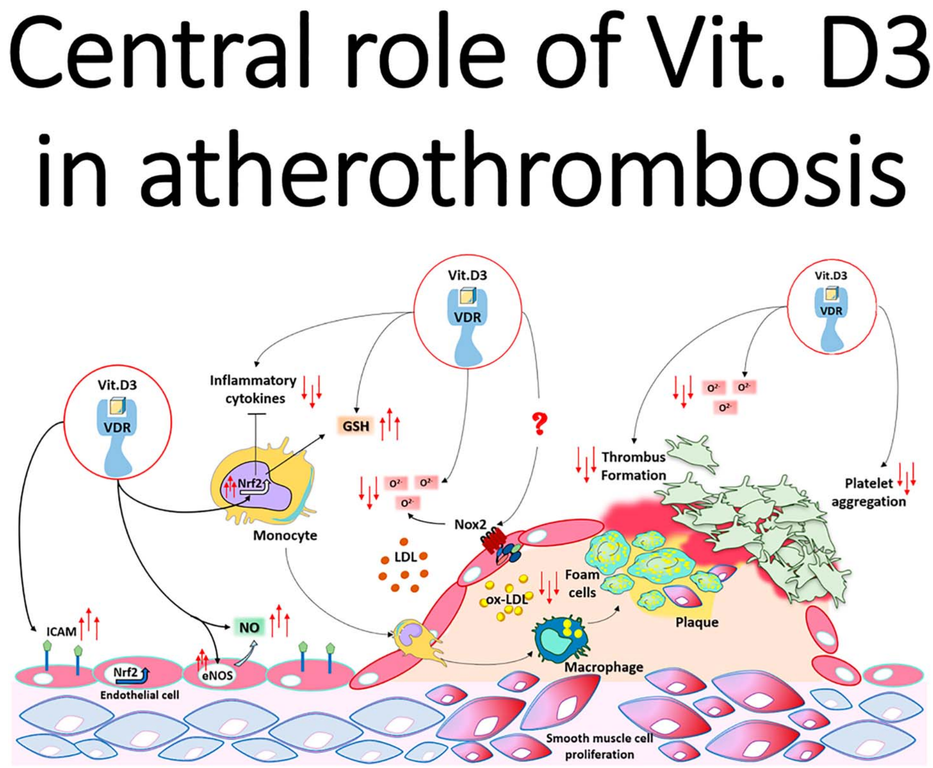

FIGURE 1. Vit.D3 exerts its biological actions in preventing atherothrombosis by binding to the VDR and favorably regulating gene expression in a pleiotropic fashion. Intracellular signaling. In particular, VDR-bound Vit.D3 could (1) increase NO production by the upregulation of eNOS; (2) downregulating endothelial ICAM expression; (3) increasing nuclear respiratory factor 2 (Nrf2) expression, which is a key transcriptional factor that suppresses ROS production from various sources, inhibits proinflammatory cytokine production, and upregulates the expression of antioxidative enzymes; (4) downregulating NOX2 activity; (5) reducing ox-LDL formation; (6) inhibiting platelet aggregation and thrombus growth. eNOS, endothelial NO synthase; GSH, gluthatione; ICAM, intercellular adhesion molecule; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NOX2, NADPH oxidase; ROS, reactive oxygen species; VDR, vitamin D receptor; Vit.D3, vitamin D3.

endothelial nitric oxide synthase expression and nitric oxide production, thereby promoting vasodilation.[2]

Supplementation of vitamin D is common, regarding the "traditional" roles of vitamin D with its positive effects on bone mineral density, for the prevention and treatment of osteoporosis. Conversely, regarding the nontraditional role of vitamin D associated with other risks, such as colorectal cancer, diabetes mellitus, multiple sclerosis, impaired immune response, and several effects on the cardiovascular system, the data in the literature are controversial. For example, Manson et al in a recent randomized clinical trial on a total of 25,871 participants concluded that supplementation with vitamin D3 at a dose of 2000 IU per day and marine n-3FAs at a dose of 1 g per day among men and women aged 55 years or older did not result in a lower incidence of cardiovascular disease. In particular, daily high-dose vitamin D supplementation for 5 years among initially healthy adults did not reduce incidence of cancer or major cardiovascular events.[7]

In addition, Güttler et al in a systematic analysis of the currently available literature showed that vitamin D or omega-3 fatty acid supplementation had no benefits for the treatment and prevention of CVDs. The authors argue that the failure of treatment with vitamin D or omega-3 fatty acids was the inadequate dosage of these substances.

Conversely, Jamilian et al demonstrated that cosupplementation for 6 weeks of 50,000 IU vitamin D every 2 weeks, plus 1000 mg of omega-3 fatty acids twice a day, had beneficial effects on fasting plasma glucose, serum insulin levels, homeostatic model of assessment for insulin resistance, quantitative insulin sensitivity check index, serum triglycerides, and very-low-density lipoprotein cholesterol levels in patients with gestational diabetes. However, the effects of vitamin D3 supplements, omega-3 fatty acids supplements, or their combinations on the risk of cardiovascular disease are still unclear, particularly in people with VDD.

In this issue of the Journal, Mehdawi et al[8] reported a randomized clinical trial conducted on Jordanian participants with VDD with no other medical conditions, to evaluate the combined effect of 1,25-dihydroxy vitamin D3 and omega-3 fatty acid supplements (D+) on Ox-LDL and non–high-density lipoprotein cholesterol levels, which are established predictors of cardiovascular disease. Participants were randomized into 4 groups as follows: (1) a control group (C) that received no supplementations; (2) a group that received 50,000 IU of vitamin D3 every week; (3) an omega-3 fatty acid group that received 300 mg of omega-3 fatty acid every day; and (4) a group that received a combination of both supplements, with the same dosage administered by the previous groups. All supplementations were administered orally for 8 weeks and a follow-up of 10 weeks. The authors demonstrated that a high dose of vitamin D3 supplement alone or in a combination with omega-3 fatty acid at 10 weeks of follow-up significantly increased non–high-density lipoprotein cholesterol and decreased serum Ox-LDL-C levels in people with VDD.[8]

Although the authors demonstrate that the combination of vitamin D3 and omega-3 fatty acid specifically reduce ox-LDL, the mechanism of action needs further clarification. In particular, the inflammatory state and oxidative stress have a fundamental role in CVDs, such as atherosclerotic process;

thus, additional studies assessing inflammatory cytokines and/or oxidative stress such as Nox2 activation, a key enzyme in the production of oxidative stress,[9] will also be helpful to understand the impact that vitamin D has on atherosclerotic mechanisms (Fig. 1). Thus, treatment with vitamin D with or without omega-3 fatty acid in VDD patients may not only improve vitamin D3 levels but also reduce future atherothrombotic events reducing the risk of cardiovascular disease.

We look forward to further studies from this group or other researchers clarifying these issues and believe that this supplementation should be recommended as a routine therapy for primary or secondary prevention of cardiovascular disease, especially when the cumulative risk burden is moderate to high.[10] Furthermore, additional mechanistic and animal studies are warranted to investigate the therapeutic potential of vitamin D3 supplements alone or in a combination with omega-3 fatty acids.

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