REVIEW ARTICLE

Vitamin D Deficiency & Cardiovascular Manifestations : A Comprehensive Review

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Vitamin D is likely one of the oldest hormones, having existed for at least 750 million years (1). Studies have demonstrated that low levels of vitamin D represent a problem of global dimensions (2). A recent Workshop Consensus for Vitamin D Nutritional Guidelines estimated that approximately 50% and 60% of the elderly in North America and the rest of the world, respectively, do not have satisfactory vitamin D levels (3). The situation is similar in younger subjects. Reasons for this widespread deficiency remain unclear but are likely related to factors such as urbanization, demographic shifts, decreased outdoor activity, air pollution and global dimming, as well as decrease in the cutaneous production of vitamin D with age. There are 2 major forms of vitamin D, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is found in plants and can be consumed in fortified foods or as a supplement. Vitamin D3 is obtained from either dietary sources or through the conversion of 7-dehydrocholesterol in the skin upon exposure to ultraviolet B (UVB) radiation. Calcitriol acts in an endocrine manner to regulate calcium metabolism by enhancing intestinal calcium absorption and mobilizing calcium from the skeleton (4,5,6).

Serum Levels of Vitamin D: Although 1,25(OH)2D is considered to be the active form of vitamin D, its levels in the serum do not correlate with overall vitamin D status, whereas the 25(OH)D level is a more clinically relevant marker. Vitamin D activity is measured in ng of 2 5(OH)D (1 ng = 40 International Units, IU). The minimum desirable serum level of 25(OH)D has been suggested to be 20-30 ng/mL according to the consensus conference (3). A 25(OH)D of < 20 ng/mL is associated with suppressible levels of parathyroid hormone when challenged with pharmacologic dosages of vitamin D. Parathyroid hormone levels begin to reach their nadir when the 25(OH)D levels are > 30 ng/mL. Intestinal calcium absorption in adults is maximized when 25(OH)D is > 30 ng/mL. Thus, many experts define vitamin D deficiency, insufficiency, and sufficiency as levels of < 20, 21 to 29, and > 30 ng/mL, respectively. To achieve these levels, a minimum of 1000 IU of vitamin D2 or vitamin D3 is needed daily when sun exposure is either unavailable or inadequate for producing vitamin D3, such as during the winter or when a sunscreen is used (7,8,9).

According to recent studies, a vitamin D deficiency [serum 25(OH)D <20 ng/mL] is likely to be an important etiological factor in the pathogenesis of many chronic diseases. These include bone mineralization disorder, a myopathy with proximal muscle weakness and muscle pain, autoimmune diseases (e.g., multiple sclerosis, type 1 diabetes) inflammatory bowel disease (e.g., Crohn disease), infections (such as infections of the upper respiratory tract), immune deficiency, cardiovascular diseases (e.g., hypertension, heart failure, sudden cardiac death), cancer (e.g., colon cancer, breast cancer, non-Hodgkin's lymphoma) and neurocognitive disorders (e.g., Alzheimer disease). (10-18)

Relationship Between Vitamin D Deficiency Between Vitamin D Deficiency and Cardiovascular Disease : Low levels of 25(OH)D have been linked to the presence of cardiovascular disease, hypertension, and the metabolic syndrome (19-22). It is still unclear whether supplementation with vitamin D is beneficial to cardiovascular health. A deficiency of vitamin D [25(OH)D <20 ng/mL or 50 nmol/L] significantly increases overall and cardiovascular mortality. The vitamin D receptor is present in endothelium, vascular smooth muscle, and cardiomyocytes and may protect against atherosclerosis through the inhibition of macrophage cholesterol uptake and foam cell formation, reduced vascular smooth muscle cell proliferation, and reduced expression of adhesion molecules in endothelial cells and through inhibition of cytokine release from lymphocytes.(23,24) In the Intermountain Heart Collaborative Study, A 25(OH) D level <15 ng/mL compared with a 25(OH)D levels >30 ng/mL was associated with a highly significant increase in the prevalence of type 2 diabetes, high blood pressure,

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dyslipoproteinaemia, peripheral vascular diseases, coronary heart disease, myocardial infarction, cardiac insufficiency and stroke ($P < 0.0001$) as well as in the incidence of overall mortality, cardiac insufficiency, coronary heart disease / myocardial infarction ($P < 0.0001$), stroke ($P = 0.003$), and their combination ($P < 0.0001$). (25, 26)

A systematic review and a meta-analysis conclude that vitamin D lowers systolic blood pressure by - 6.18 mmHg and reduces diastolic blood pressure by - 3.1 mmHg in hypertensive patients. No change in blood pressure was observed in normotensive persons.(27) Black US. Americans suffer significantly more frequently from high blood pressure than whites. Reduced blood levels of 25(OH)D could be responsible for the higher risk of hypertension, since people with darker skin color generally produce less vitamin D3 in the skin due to the higher content of melanin and thus have lower levels of 25(OH)D.

The suppression of parathyroid hormone (PTH) by vitamin D, which has been known for some time, must now be seen in a new light, since PTH has been increasingly recognized in recent years as a major risk factor for cardiovascular diseases such as high blood pressure or cardiac insufficiency. PTH can cause damage to the cardiovascular system at different levels, either directly or indirectly. Elevated PTH levels, as well as a hypercalcaemia, can promote the development of hypertension. In addition, hyperparathyroidism is associated with a high incidence of hypercontractility of the heart muscle with consecutive left ventricular hypertrophy and calcification of the myocardium. Vitamin D counteracts these processes, in that it, among other things, promotes the synthesis of anti-inflammatory cytokines, such as interleukin 10, and of other substances that reduce vascular calcification (e.g., matrix Gla protein). In addition, vitamin D counteracts the adverse effects of the so-called "advanced glycatione ndproducts" (AGEs) on the endothelium (28)

Treatment Strategies

Sensible sun exposure is the least expensive and most efficient way of obtaining an adequate amount of vitamin D. It has been estimated that a healthy adult in a bathing suit exposed to one minimal erythemal dose (MED) of sunlight is equivalent to ingesting about 20 000 IUs of vitamin D.(4) Thus the skin has a large capacity to produce vitamin D. Because time of day, season of the year and latitude along with degree of skin pigmentation has a dramatic effect on the cutaneous production of vitamin D there is no simple recommendation as to how much time to be exposed to obtain an adequate amount of vitamin D. However for example if a person knows that they are going to get a light pinkness to their skin 24 h later, i.e., a MED, by being exposed to 30 min of sun in their locale, the recommendation is to expose arms, legs and abdomen and back when possible for about 10-15 min followed by good sun protection. One way to determine how much vitamin D a child or adult is producing is to use a free app dminder.info which not only provides the user with how much vitamin D they are producing but also tells them when to stop being exposed to sunlight without sun protection to prevent sunburn. Oral vitamin D (vitamin D2 or D3) can be taken on an empty stomach or with a meal. Both vitamin D2 and vitamin D3 at physiologic doses are effective in raising the blood level of 25(OH)D.(29) The meal does not need to contain fat in order for fat-soluble vitamin D to be absorbed. Furthermore vitamin D can be taken daily or the total amount can be taken once a week or even once a month as long as the total is the same i.e., 3000 IUs daily or 21 000 IUs weekly or 90 000 IUs monthly are equally effective in maintaining serum 25(OH)D levels in the desired range of 40-60 ng/mL. To guarantee vitamin D sufficiency there are a variety of strategies to both treat and prevent vitamin D deficiency. One simple strategy that is effective is to fill the empty vitamin D tank with 50 000 IUs of vitamin D once a week for 8-12 weeks.(29) This is equivalent to ingesting approximately 6600 IUs daily. To prevent recurrence of vitamin D deficiency 50 000 IUs of vitamin D once every 2 weeks (equivalent to 3300 IUs daily) forever is effective in maintaining a healthy vitamin D status without causing toxicity. Even young children have been effectively treated for vitamin D deficiency with 50 000 IUs of vitamin D weekly for 6 weeks or 2000 IUs of vitamin D daily.(30)

Conclusion

On the basis of this review, hypovitaminosis D has been observed worldwide, and many studies have demonstrated a strong association between vitamin D status and systemic diseases like coronary artery disease, hypertension, diabetes and metabolic syndrome. In the meantime, health professionals should be aware of the potential negative implications of vitamin D insufficiency and make recommendations for their patients to improve their vitamin D status. However, definitive randomized controlled trials are still needed to determine whether vitamin D therapy is beneficial to preventing cardiovascular disease. Given the low cost, safety, and demonstrated benefits of higher 25(OH)D concentration, vitamin D supplementation should become a public health priority to combat these common and life threatening diseases.

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