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Cardiovascular Diease and Vitamin D Deficency

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Cardiovascular Disease

And

Vitamin D Deficiency

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Abstract

Vitamin D deficiency is a common health condition affecting a significant number of individuals throughout the world. For years vitamin D has generated interest in reducing osteoporosis because of its role in bone and calcium metabolism. Recently low concentrations have been linked to the development of several cardiovascular diseases such as hypertension, heart failure, atherosclerosis and peripheral arterial disease. The purpose of this article is to examine evidence regarding vitamin D deficiency and cardiovascular disease and provide advanced practice nurses with recommendations regarding supplementation in those individuals with vitamin D deficiency and risk for development of cardiovascular disease.

Keywords: vitamin D deficiency, 25-hydroxyvitamin D, cardiovascular disease, vitamin D and cardiovascular events.

Cardiovascular disease (CVD) is a common cause of mortality and morbidity within the United States (U.S.) resulting in nearly 2,400 deaths per day and an estimated 2009 economic cost of $475.2 billion.[1, 2] CVD includes a variety of illnesses such as coronary artery disease, peripheral arterial disease, left ventricular hypertrophy and congestive heart failure.[3] While genetics play a significant role, factors such as poor diet, inactivity and increased life expectancy may contribute to further development of CVD.

Vitamin D deficiency (defined as 25-hydroxyvitamin D [25(OH)D] of less than 20ng/mL) is a common yet easily treatable worldwide health condition affecting approximately 30 to 50% of individuals throughout the U.S. and many nations.[4] Evolving data suggest adequate levels of vitamin D are important not only for bone health but for non-skeletal roles such as cardiovascular health.[5] Vitamin D deficiency has the potential to be a significant public health concern since low concentrations have been associated with the development of hypertension, heart failure, atherosclerosis and peripheral arterial disease.[4,6, 7]

For years vitamin D has sparked interest within medical and lay communities because of its potential in reducing osteoporosis. Healthcare providers have long understood the role vitamin D plays in metabolism of bone and calcium however the association between vitamin D deficiency and CVD is not universally understood.[4, 8] Therefore, the purpose of this article is to examine evidence regarding vitamin D deficiency and cardiovascular disease. The evidence is intended to provide advanced practice nurses with recommendations for practice regarding vitamin D supplementation in individuals with hypovitaminosis D and risk for CVD.

Forms of vitamin D

Vitamin D is a fat soluble secosteroid molecule associated with metabolism of bone and calcium.[9] Circulating vitamin D is present in two interchangeable forms, vitamin D_2

(ergocalciferol) and vitamin D_3 (cholecalciferol).[10] Vitamin D_2 is the result of ergosterol irradiation from yeast and is obtained through dietary consumption of plants, plant materials, fortified foods (milk, cereals, orange juice) and dietary supplementation. [11, 12] Vitamin D_3 is formed within the skin through sunlight or ultraviolet light irradiation of 7-dehydrocholesterol and is obtained through food sources such as fatty fish (herring, tuna, wild or farm salmon), egg yolks, fortified foods or dietary supplementation.[13]

Vitamin D Physiology

The parathyroid hormone (PTH) along with calcium and phosphorus regulates the production and conversion of vitamin D.[14] In the liver, the biologically inactive pro-hormone of vitamin D is enzymatically converted to its major circulating form 25(OH)D by vitamin D 25-hydroxylase (CP27A1). [14, 15] The main metabolizer of 25(OH)D is the kidneys, here circulating vitamin D is converted to its active hormonal form calcitriol [$1,25(OH)_2D_3$] by the enzyme *1a*-hydroxylase (CYP27B1).[14, 15]

Within target cell nuclei, vitamin D receptors (VDRs) utilize calcitriol to facilitate interactions within cell DNA.[14,16] VDRs combine with retinoic X receptors and then bind with $1,25(OH)_2D_3$ to form a heterodimer complex. This heterodimer complex attaches to vitamin D responsive elements on DNA responsive genes to alter gene expression.[14, 16] 25(OH)D tightly regulates this interaction and low concentrations can result in altered gene expression.[17]

Vitamin D Sources

Sunlight provides the major source of vitamin D and skin has a great capacity of producing vitamin D_3. Approximately 80-90% of cholecalciferol bioavailability is via cutaneous synthesis from UVB irradiation.[14] Sunlight exposure is necessary for production of vitamin D. Variables which affect production of vitamin D include the strength of UBV rays, the amount of time spent

in the sun, the latitude of the earth on which the person lives, time of year, types of clothing worn, high air pollution levels and the degree of pigment in the skin.[14, 18] It is estimated 5 to 30 minutes of mid-day (10am to 3pm) summer sunlight exposure twice weekly to the arms and legs of light skinned Caucasian individuals is sufficient to prevent vitamin D deficiency.[18] Tanning beds are not a reliable source of cholecalciferol as they do not produce the same levels of UVB rays as natural sunlight.[18]

The remaining 10-20% of vitamin D_3 is obtained through dietary consumption.[14] Oily fish (herring, sardines, tuna or salmon), fish liver oils, fortified foods (milk, yogurt, cereal, orange juice), egg yolks and oral vitamin supplementation provide an excellent dietary source of vitamin D.[13, 19] Because of the many variables on cholecalciferol production, the practitioner will frequently encounter deficiencies due to inadequate sun exposure and inadequate dietary intake that may need to be supplemented through dietary intake of fortified foods or vitamin supplementation.

Assessing Vitamin D Level

Measuring the active form of vitamin D [$1,25(OH)_2D_3$] is not beneficial in determining vitamin D status due to the short half-life of this form.[18] Thus measurement of total 25(OH)D level reflects true cutaneous synthesis, dietary intake or supplementation and is considered the "hallmark" for determining vitamin D deficiency, insufficiency, adequacy and toxicity.[20]

When assessing an individual's vitamin D level and/or nutritional status, the definition of vitamin D deficiency has caused much debate. However, most experts define vitamin D deficiency as levels less than 20ng/mL, insufficiency as levels between 21-29ng/mL and the wide "optimal" range of adequacy between 30 and 50ng/mL. Levels between 50-150ng/mL are indeterminate and possibly harmful. Levels greater than 150ng/mL are considered toxic.[1, 21, 22]

Classic Presentation of Vitamin D Deficiency, Insufficiency, and Toxicity

Vitamin D deficiency can lead to clinical symptoms of severe hyperparathyroidism, calcium malabsorption, rickets, osteomalacia and myopathy.[23] Insufficiency may lead to mild hyperparathyroidism, low intestinal calcium absorption and subclinical myopathy.[24] Hypervitaminosis D is extremely rare but can be caused by ingestion of massive oral supplementation doses.[13] Vitamin D intoxication include signs and symptoms of hypercalcemia (anorexia, nausea, vomiting) polyuria, polydipsia, weakness, nervousness, pruritus and potentially renal failure.[9]

Risk Factors for Vitamin D Deficiency

Risk factors for vitamin D deficiency include hepatic or renal disease, highly pigmented skin resulting in less cutaneous synthesis of vitamin D, fat malabsorption syndromes, use of sunscreen protection factor of 15 or higher, medications that alter vitamin D metabolism (anticonvulsants, glucocorticoids, anti-rejections, HIV therapy) and advanced age.[14, 21, 25]

Ecological studies have reported a higher incidence of coronary artery disease and hypertension secondary to increased distance from the equator, consistent with incidence of vitamin D deficiency/insufficiency in northern latitudes.[6, 20] Figure 1 demonstrates vitamin D deficiency found in northern latitudes of the United States.[26]

Source: Time for more vitamin D
Harvard Women's Health Watch (2008) (26)
Adapted with permission

Figure 1

Additional risk factors for vitamin D deficiency includes highly polluted air resulting in more time spent indoors surrounded by high efficiency windows. This results in loss of vitamin D secondary to blocking of UVB rays.[3] Poor diet, especially in areas far from the equator also results in a greater risk of hypovitaminosis D. Individuals such as those who are homebound, wear long robes or head coverings for religious reasons and occupations which require extended periods of time spent indoors are at additional risk for vitamin D deficiency.[27]

Vitamin D Deficiency and the Cardiovascular System

For the past decade, several advances have been made in the study of vitamin D as it pertains to the cardiovascular system. Recent studies demonstrate the presence of VDRs in the heart, blood vessels, liver, immune system and skeletal muscle suggesting vitamin D plays a role in many previously unknown biochemical pathways. [12] Data suggests a higher percentage of patients presenting with myocardial infarction, stroke, heart failure, diabetes, coronary artery disease, and peripheral arterial disease have a higher incidence of vitamin D deficiency.[28,29,30]

Mechanisms by which vitamin D directly influence the development of cardiovascular disease may include reduction in inflammation, suppression of the renin-angiotensin system, and alteration of cardiovascular remodeling [16, 31] Studies indicate 25(OH)D serum levels are inversely associated with blood pressure or plasma renin activity in normotensive and hypertensive subjects.[14]

Promising data obtained from cohort studies and randomized control trials confirm the benefit of vitamin D in the reduction of blood pressure and on cardiovascular health.[22] Low levels of 25(OH)D have been found to increase systemic inflammation and parathyroid hormone levels. This results in increases in both blood pressure and myocardial contractility, which eventually

leads to left ventricular hypertrophy, vascular remodeling, congestive heart failure and chronic vascular inflammation.[4, 7, 32]

Vitamin D and Cardiovascular Disease

Using data obtained from the Third National Health and Nutrition Examination Survey (NHANES III) 2001-2004[33], a cross-sectional study was conducted to examine the relationship between cardiovascular disease and hypovitaminosis D in 8,351 adults with coronary heart disease, heart failure, stroke, and peripheral arterial disease.[34] Results of the study found cardiovascular diseases were more prevalent in adults with lower 25(OH)D levels.

Hypovitaminosis D was also more common in subjects with certain cardiac disease such as coronary heart disease and heart failure.[34] Additional data obtained from NHANES III[33] found a higher incidence of vitamin D deficiency in adults with ischemic heart disease and stroke when compared to adults without ischemic heart disease and stroke.[16]

Low vitamin D status has been associated with increased coronary plaque levels. Observational studies reported an inverse relationship between 1,25(OH)2D levels and coronary calcification in 173 individuals at moderate to high risk for coronary disease.[16] A multi-ethnic study of nearly 1400 participants demonstrated 25(OH)D levels were associated with reduced rates of coronary calcification.[16] Observational studies have also suggested poor vitamin D status is associated with higher incidence of coronary artery disease.[9]

Vitamin D and Cardiovascular Events

Almost 1 out of every 3 individuals dies from cardiovascular disease in the United States. Accumulating data links vitamin D deficiency to cardiovascular events suggesting an association between cardiovascular events and vitamin D deficiency.[35] Analysis of a prospective observational study conducted of 35,716 participants followed from 5 to 27.1 years for incident

cardiovascular events or deaths demonstrated vitamin D deficiency is associated with a modest increased risk of cardiovascular events.[35]

A study of 6,219 men and women greater than 30 yrs of age who were free from cardiac disease at baseline was conducted to evaluate correlation between low vitamin D levels and increased risk for developing cardiovascular disease.[7] Follow-up identified 293 cerebrovascular disease deaths and 640 coronary disease deaths. The study concludes low circulating levels of vitamin D may predict a higher risk of cardiovascular disease deaths. Subjects with the "highest quintile of serum 25 (OH)D levels had less than half the risk of cerebrovascular death as those in the lowest quintile".[7]

The Framingham Offspring Study followed 1739 participants without prior cardiovascular disease for a 5 year period.[16] Serum 25(OH)D levels were measured for a 5 year period in order to determine cardiovascular risk and events. The study demonstrated the highest risk of developing a first cardiovascular event was in participants with severe vitamin D deficiency and hypertension.[16, 18]

Vitamin D and Hypertension

A major cardiovascular risk factor is essential hypertension. Vitamin D and blood pressure control appears to be related via multiple pathways and is inversely related to serum renin activity.[9] Studies in mice verify lack of vitamin D receptor activation influences tonic upregulation of the renin-angiotensin system.[36] Cross-sectional studies have shown vitamin D deficiency is associated with hypertension supporting epidemiological observations that hypertension is due in part to a deficiency in vitamin D.[23] Though researchers acknowledge the exact means by which adequate vitamin D status may protect against cardiovascular disease are

not fully appreciated, experimental studies indicate vitamin D is one of the most potent hormones for suppressing the renin-angiotensin system and blood pressure regulation.[7, 9, 18]

Vitamin D and other Co-existing Chronic Diseases

Cross-sectional studies reveal an associated between low vitamin D levels and stroke, peripheral artery disease, heart failure, diabetes, insulin resistance and metabolic syndrome. A study of 83,779 women was conducted with baseline and 20 year follow-up of vitamin D and calcium intake.[23] A 33% lower risk of type 2 diabetes was associated with combined oral daily intake of 800IU of vitamin D and 1200mg of calcium. Hypovitaminosis D was also associated with increased risk of cardiovascular disease in a study of 459 outpatients with type 2 diabetes. Observational studies also suggest oral supplementation of vitamin D may protect not only against type 2 but type 1 as well.[23]

A study of 15,088 adult male and females over the age of 20 years examined the correlation between serum 25 (OH)D levels and cardiovascular disease risk factors. Obtained data demonstrated vitamin D deficiency has been associated with congestive heart failure whereas increased blood levels of 25(OH)D have been associated with decreased blood pressure.[30]

Recommended Dietary Allowance

Traditionally up to 95% of vitamin D requirements are the result of synthesis in the epidermis through sun exposure, with the remainder coming from dietary food sources. Studies indicate the average U.S. adult consumes approximately 230 IU of vitamin D per day thus necessitating the need of supplementation.[1] In November 2010 the Institute of Medicine revised upward the recommended dietary allowance for vitamin D intake.[25] Current guidelines recommend 400 IU/day for neonates through 12 months of age, 600 IU/day for individuals 1-70 years of age and 800IU/day for adults 71 years of age and older.[27]

Vitamin D Screening

Although vitamin D deficiency is prevalent, universal screening for vitamin D deficiency is not supported. The U.S. Preventative Services Task Force does not comment either for or against routine screening for vitamin D deficiency. However testing patients with clinical risk factors such as decreased intake due to poor nutritional status, malabsorption, hepatic or renal disease and the aged may be beneficial.[14, 21, 25] Patients with low bone mineral density or prior low-impact skeletal fractures should be presumed to have vitamin D deficiency. Clinical management steps should be taken to increase serum vitamin D levels, not only to reduce the risk of serious skeletal fractures but also to reduce cardiac disease risk factors.

It has been recommended that clinicians routinely evaluate for hypovitaminosis D in patients with symptoms such as bone or muscle pain and generalized weakness. These symptoms are often associated with low vitamin D levels and might be misdiagnosed as fibromyalgia, chronic fatigue, age-related weakness, or even depression.[20]

It is also important to be aware both geographic and seasonal variability affect vitamin D levels. For example, a person living in Minnesota with an "optimal" 25(OH)D level in the summer may become "deficient" in the winter without a change in diet. In situations such as these, the clinician may adopt a vitamin D screening protocol during the winter months.[20]

Treatment Recommendations

Clinical investigations reveal the most common treatment recommendations for vitamin D deficiency are sun exposure, dietary intake and oral supplementation. However, it is difficult to safely achieve the amount of sun exposure needed for adequate vitamin D levels.[1] When sun exposure is inadequate dietary guidelines for Americans 2010 recommends nutritional needs should be met through consumption of foods abundant in vitamin D.[39] Nutrient dense foods not

only contain essential vitamins and minerals but dietary fiber which provides added health benefits.

For individuals with severe hypovitaminosis D who are unable to achieve adequate vitamin D levels through sun exposure and/or dietary intake oral supplementation may be warranted. Prescription oral supplementation of D_2 or D_3 at 50,000 IU per week for 8 to 12 weeks as an initial treatment regimen followed by re-evaluation of serum 25(OH)D levels.[1] If the vitamin D levels have not reached 30ng/mL, a second eight-week course should be prescribed followed by re-evaluation of 25(OH)D status.[1] Once levels greater than 30ng/mL have been achieved, maintenance therapy includes one of three options: (1) 50,000IU of D_2 every two weeks; (2) 1,000-2,000IU of D_3 daily; or (3) sunlight exposure with repeat evaluation of 25 (OH)D in three to six months.[1, 25]

Implications for NPs

As patients seek to understand the significance vitamin D has on health and well-being, APNs are at the forefront in answering questions and concerns. Because vitamin D deficiency has the potential to be a significant public health concern, APNs must be able to not only screen but appropriately treat and evaluate outcomes in those individuals with vitamin D deficiency.

While agreement regarding diagnosing vitamin D deficiency and development of a recommended treatment plan remain at a cross road, several strong studies have demonstrated a link between vitamin D deficiency and cardiovascular disease.[38] Several studies have demonstrated low 25-hydroxyvitamin D levels have been associated with cardiovascular disease. These studies do not demonstrate a direct cause/effect relationship between cardiovascular disease and vitamin D deficiency. Further prospective studies are needed to determine the role vitamin D plays in treatment or prevention of cardiovascular disease.[35]

APNs need to assess individual risk factors and screen patients at risk for vitamin D deficiency within the primary care setting. Practitioners need to keep in mind treating vitamin D deficiency does not replace evidence based practice treatment of cardiovascular disease. However, screening for vitamin D deficiency may be a valuable tool in patients with risk factors for vitamin D deficiency and history of cardiovascular disease, peripheral arterial disease, stroke, and congestive heart failure.

Conclusion

Health benefits of vitamin D have long been established in regards to bone health. Recent evidence suggests an association between vitamin D deficiency and increased risk for development of cardiovascular disease. Vitamin D deficiency is easy to screen for but it is not yet widely accepted in clinical practice. Despite growing attention to this deficiency there are no established guidelines to assist clinicians in determining which patients warrant screening especially with regards to using it as a marker for establishing cardiovascular disease risk. However, a large volume of experimental and clinical evidence points toward a link between vitamin D deficiency and several cardiovascular conditions. As we continue to explore the arena of vitamin D deficiency in relation to increased cardiovascular disease, monitoring 25(OH)D levels and supplementing levels less than 20ng/mL is recommended for optimal bone and general health. As new studies linking vitamin D deficiency with cardiovascular disease are published clinicians will have another important reason to assess and treat their patients who have vitamin D deficiency.

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