

Nonskeletal Benefits of Vitamin D: Beyond the Media Hype

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The nonskeletal benefits of vitamin D supplementation may include improved cardiac health and improved neuromuscular function in older adults.

For many years, researchers have studied the numerous benefits of vitamin D supplementation. It is well known that vitamin D plays an important role in the skeletal development of children and maintenance in adults, but recently vitamin D has been found to play a possible role in the pathogenesis of several disease processes. Numerous epidemiologic studies have shown that people who live at higher latitudes have an increased risk for many chronic conditions, including cardiovascular disease (CVD), diabetes, and common cancers such as breast, colon, and prostate.^{1,2}

Since the advent of gas chromatography mass spectrometry as a better means to determine patient vitamin D status, the prevalence of vitamin D deficiency and the benefits of supplementation are more impressive than previously thought.³ The purpose of this article is to review several of the nonskeletal benefits of vitamin D supplementation, including improved cardiac health, improved neuromuscular function in older

adults, and cancer risk reduction. There is limited evidence that is gender specific to women in regards to CVD and neuromuscular function. The effects of vitamin D supplementation specifically on women is discussed in each section where data are available.

CARDIOVASCULAR DISEASE

CVD has become one of the major causes of mortality and morbidity worldwide. Recent evidence suggests that vitamin D deficiency may adversely affect cardiovascular health and predispose patients to hypertension, coronary artery disease, congestive heart failure, and diabetes mellitus.⁴ Epidemiologic studies have shown that living at higher latitudes and inadequate vitamin D and calcium levels are associated with coronary risk factors and increased risk for adverse cardiovascular events.⁵

Vitamin D deficiency has been well documented in patients with hypertension, stroke, congestive heart failure, and peripheral artery disease.⁴ The relationship between cardiovascular risk factors and vitamin D levels was observed in 16,603 men and women using the National Health and Nutrition Examination Survey databases.⁶ In this cross-sectional study, those subjects with vitamin D deficiency, after adjustment for age, gender, and race/ethnicity, had a greater incidence of ischemic heart disease and stroke. The Framingham Offspring Study found that men and women with serum 25(OH)D levels less than 15 ng/mL have a 60% to 80% increased risk for CVD than those with higher levels.⁵ Furthermore, a recent meta-analysis found a 74% prevalence of vitamin D deficiency among patients with coronary artery disease and congestive heart failure.⁷

FOCUSPOINT
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FOCUSPOINT

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Vitamin D supplementation may correlate with a decrease in cardiovascular risk factors. In 2007, a meta-analysis of 18 randomized controlled trials consisting of 57,000 subjects showed that a vitamin D intake of up to 500 IU/day seemed to be associated with a reduction in total mortality rates by 7%, in part by decreasing cardiovascular deaths.⁸

The data on cardiovascular health have shown calcium plus vitamin D supplementation to be superior to that of calcium supplementation alone. In a randomized controlled trial, 148 women older than 70 with vitamin D levels lower than 20 ng/mL were randomly assigned to receive 1,200 mg calcium per day or 1,200 mg calcium plus 800 IU vitamin D per day. Within 8 weeks of supplementation, the systolic blood pressure in the vitamin D group decreased by an average of 13 mm Hg.⁹

A Harvard cohort study, the Nurses' Health Study II, further demonstrated an inverse association between vitamin D levels and the incidence of hypertension.¹⁰ Women in the lowest quartile of 25(OH)D (median 16.7 ng/mL) compared with the highest quartile of 25(OH)D (median 37.9 ng/mL) had an increased odds ratio (OR) of incident hypertension: OR of 2.21 (95% CI, 1.57-3.12; $P < .001$).

Despite this convincing data, the largest and longest trial, the Women's Health Initiative, combined low-dose vitamin D₃ (400 IU/d) and calcium carbonate supplementation (1,000 mg/d) and found no effect on self-reported incident hypertension after 7 years of follow-up.¹¹ Thus, the causal relationship between vitamin D supplementation and CVD has not been demonstrated in randomized trials.

NEUROMUSCULAR FUNCTION

Falls among elderly patients continue to be a common cause of morbidity and mortality. In 2006, it was estimated that falls occur in 30% of community-dwelling patients and up to 50% of institutionalized older adults, resulting in approximately 16,000 deaths.¹²

Several studies support the hypothesis that vitamin D insufficiency contributes not only to increased risk for fractures but also to muscle weakness and subsequent falls in older persons. Binding of vitamin D to its receptor on muscle promotes protein syn-

thesis and muscle cell proliferation and differentiation.¹³ Atrophic type II muscle fibers, those which are recruited first to prevent a fall, have been found on muscle biopsies of patients with a decreased serum 25(OH)D.¹³ Furthermore, vitamin D-deficient patients have decreased proximal (hip) muscle strength that affects gait stability and predisposes the elderly to falls.¹⁴

Vitamin D supplementation may reduce the risk for falls in the elderly by improving muscle strength and lower extremity function. A meta-analysis performed by O'Donnell et al found a 34% decreased risk for falling in the active vitamin D-treated group than in the placebo group.¹⁵ A recent 3-year randomized controlled trial showed an even more protective effect of vitamin D plus calcium supplementation. Two hundred forty-six women 65 or older were randomly assigned to receive 700 IU vitamin D plus 500 mg calcium or placebo. The risk of falling in women who received supplementation was reduced by 46%. The fall reduction was even more apparent in women whose physical activity was below the median level and was found to be 65% decreased.¹⁶ This effect of vitamin D supplementation may lead to a substantial decrease in fall morbidity and mortality in the elderly population.

BREAST CANCER

Vitamin D has been reported to assist in the regulation of cell growth and prevention of cancer progression by increasing cell differentiation and apoptosis of cancer cells.¹⁷ Ecologic studies reveal that women residing in areas of low exposure to sunlight have a higher risk for breast cancer and increased breast cancer morbidity and mortality rates.¹⁸

A meta-analysis done by Garland et al suggested a relationship between vitamin D intake and breast cancer risk by measuring serum 25(OH)D levels.¹⁹ Women were divided into quintiles based on 25(OH)D levels. In patients with 25(OH)D levels above 52 ng/mL, there was a 50% reduction in breast cancer risk when compared with those women with levels lower than 10 ng/mL. This was further supported by another meta-analysis of 11 studies that showed a 45% decrease in breast cancer in patients with the highest quintile of circu-

lating 25(OH)D.²⁰

Several studies have reported an inverse association between vitamin D and/or calcium intake and breast cancer risk. A recent case-control study was done on 6,500 Canadian women ages 25 to 74, half of whom were diagnosed with breast cancer. The researchers found that vitamin D supplementation greater than 10 mcg/day (4,000 IU/d) reduced the breast cancer risk by 24%.²¹

In a randomized controlled trial by Lappe et al, the incidence of breast cancer was evaluated in postmenopausal women randomly assigned to receive 1,500 mg supplemental calcium per day alone, supplemental calcium and 1,100 IU vitamin D per day, or placebo.²² In comparison to the placebo group, the researchers reported a significant reduction of cancer risk in the calcium and vitamin D group (relative risk [RR], 0.4) and for the calcium-only group (RR, 0.53).

There is limited evidence that suggests the relationship between supplemental vitamin D and breast cancer risk differs depending on menopausal status. A prospective cohort study done by Lin et al showed that higher intakes of vitamin D and calcium in premenopausal women, but not postmenopausal women, resulted in a lower risk for breast cancer, specifically the more aggressive cancer types.²³

Similarly, vitamin D intake and risk for breast cancer was assessed in the Nurses' Health Study I.²⁴ Among premenopausal women, there was an inverse linear dose-response relationship between total vitamin D intake and RR for breast cancer. Women who consumed a mean of >500 IU per day had a 28% decreased risk for breast cancer (RR, 0.72; 95% CI, 0.55-0.94; $P = .01$). There was no significant association between total or dietary vitamin D intake for postmenopausal women.

Additionally, in the Women's Health Initiative trial, 36,000 postmenopausal women were randomly assigned to 1,000 mg calcium plus 400 IU vitamin D daily versus placebo.²⁵ There was no difference between the 2 groups in terms of the incidence of invasive breast cancer.

Overall, these findings suggest the possible importance of vitamin D and calcium supplementation in the prevention of breast cancer. However, the optimal level of serum 25(OH)D

has yet to be identified. Garland et al propose that a serum 25(OH)D level of 50 ng/mL may be required to result in a near 50% reduction of breast cancer risk when compared to patients with vitamin D deficiency, particularly when sunlight exposure is minimal.¹⁹ In order to attain and maintain this level, it is suggested that patients would require 4,000 IU of total daily vitamin D via diet, supplements, and/or sun exposure.¹⁹

EXCESS VITAMIN D AND PANCREATIC CANCER RISK

Although some evidence suggests that vitamin D may provide protection against certain cancers such as breast cancer, the evidence of potential benefit is limited and inconsistent. There is also a lack of data in the understanding of the role of vitamin D in carcinogenesis. Moreover, some studies have suggested the possibility that higher vitamin D levels are associated with an increased risk for some cancers, including pancreatic cancer.

A pooled, nested, case-control study of data from 8 cohorts demonstrated a statistically significant 2-fold increased risk for pancreatic cancer among patients with circulating 25(OH)D concentrations 100 nmol/L (40 ng/mL) or higher, as compared with those with concentrations of 50 to 75 nmol/L (20 to 30 ng/mL).²⁶ The National Cancer Institute, therefore, does not recommend for or against the use of vitamin D supplements in healthy patients to reduce the risk of cancer.

OPTIMAL VITAMIN D CONSUMPTION

Vitamin D has been shown to play an important role in the prevention of many chronic diseases, in addition to proper muscle functioning in older adults. However, the actual recommended daily allowance (RDA) of vitamin D and the serum 25-OH level to attain these desirable health outcomes remain controversial. To address this issue, the Institute of Medicine (IOM) recently released its recommendations regarding vitamin D and calcium supplementation.²⁷ Per this study, a 25-OH level between 20 and 50 ng/mL is sufficient, with an RDA for vitamin D of 600 IU for women up to the age of 70 and 800 IU for those older than 70.

The American Association of Clinical Endocrinologists subsequently released a

FOCUSPOINT
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statement recommending a 25-OH level of 30 to 50 ng/mL, with 1,000 to 2,000 IU of vitamin D daily to maintain that 25-OH level. In addition, the upper limit of safe consumption for vitamin D according to the IOM has been set to 4,000 IU.²⁷ Although research into vitamin D's possible roles in diseases is conflicting, the risk for vitamin D toxicity is minimal when intake is 2,000 IU or less, while the benefit to patients may be substantial.

CONCLUSION

This article reviews the nonskeletal benefits of vitamin D supplementation to target a serum vitamin D level in the normal range (ie, >30 ng/mL). The IOM acknowledges that there is a lack of data to recommend higher amounts of vitamin D supplementation. Further randomized controlled studies are required to determine the exact dose of vitamin D necessary to optimize the potential beneficial effects reviewed here, while minimizing risks to patients.

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