Deficient 25-Hydroxyvitamin D Levels Are Associated with Incident Cardiovascular Events in Men

Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-Hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med 2008;168:1174–80.

Study Overview

Objective. To determine whether levels of 25-hydroxyvitamin D (25[OH]D) are associated with incident myocardial infarctions (MIs).

Design. Nested case-control study within a prospective cohort.

Setting and participants. 51,529 male health care professionals enrolled in the Health Professionals Follow-up Survey in 1986. Of those initially enrolled, 18,225 participants provided blood samples in 1993–1995 that could be assayed for 25(OH)D. From the date of blood collection to 31 January 2004, incident cases of nonfatal MI or fatal coronary heart disease (CHD) were identified based on self-report and review of medical records by blinded reviewers, and controls were randomly selected from the cohort and matched for age, smoking status, and month of blood collection. Participants with known cardiovascular disease prior to 1994 were excluded.

Main outcome measures. Association between 25(OH)D level and incidence of nonfatal MI and fatal CHD. 25(OH)D levels were categorized as deficient (≤ 15 ng/mL), insufficient (15.1–22.5 ng/mL or 22.6–29.9 ng/mL), and sufficient (≥ 30 ng/mL). Multivariate analysis adjusted for family history of MI before age 60 years, history of diabetes or hypertension, alcohol intake, body mass index, physical activity, region, race, multivitamin use, marine omega-3 fatty acid intake, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels.

Main results. 454 cases and 900 matched controls were included in the analysis. The coefficient of variation for 25(OH)D was 11.5%, as measured in a subsample of participants with serial measurements. Case participants were significantly more likely to have a family history of MI before age 60 years, diabetes, higher body mass index, and hypertension; had higher levels of low-density lipoprotein cholesterol and triglycerides and lower high-density lipoprotein cholesterol; drank more alcohol; and were more likely to live in the Midwest. In the final model controlling for all covariates, participants with deficient levels of 25(OH)D (≤ 15 ng/mL) had a relative risk of 2.09 (95% confidence interval [CI], 1.24–3.54) of experiencing a cardiovascular event as compared with those with sufficient levels of 25(OH)D (≥ 30 ng/mL). The *P* value for trend was < 0.001 from the lowest to highest quartiles of 25(OH)D, although the relationship was not entirely linear (relative risk, 1.43 for 25[OH]D level of 15.1–22.5 ng/mL vs. 1.60 for a level of 22.6–29.9 ng/mL).

Conclusion. Deficient 25(OH)D levels are associated with incident nonfatal MI or fatal CHD.

Commentary

Cardiovascular-related mortality is highest in winter months, at lower altitudes, and at higher latitudes [1]. These findings have led to the hypothesis that vitamin D deficiency, which is associated with these same geographic and seasonal risk factors, could be related to cardiovascular disease. Prior case-control studies have found that vitamin D levels are lower in patients with angina or MI compared with control patients [2,3]. Biologic plausibility for prevention of cardiovascular events is also evident because vitamin D can favorably affect the renin-angiotensin system by suppressing renin synthesis [4,5], decreasing inflammation [6], and influencing both vascular smooth muscle proliferation and vascular calcification [1].

The results of this study by Giovannucci et al are provocative and, when considered in conjunction with prior observational studies, suggest that 25(OH)D has a true effect on cardiovascular disease. However, the results are not entirely clear in this study. There was no clear dose-response between 25(OH)D level and occurrence of a cardiovascular event. Individuals with a 25(OH)D level of 22.6 to 29.9 ng/mL had higher rates of cardiovascular events than those with a 25(OH)D level of 15.1 to 22.5 ng/mL, although this is probably not statistically significant (statistical comparisons were not provided for all between-group comparisons). Additionally, because this is an observational study and several differences are present between cases and controls, unmeasured confounding is a strong possibility. The lack of diversity in the sample is also a limitation given that the results are only pertinent to male health professionals.

More disappointing is the result of the largest randomized

clinical trial to date that evaluated the impact of vitamin D supplementation on mortality. The Women's Health Initiative randomized 36,282 postmenopausal women to calcium plus vitamin D or placebo and found no difference in the incidence of mortality from MI or CHD [7]. Giovannucci et al suggest that supplementation in this trial was too limited, especially because the increased risk of a cardiovascular event is most evident for those in the lowest 25(OH)D quartile compared with the highest quartile, a difference of at least 15 ng/mL. They suggest that much more aggressive supplementation might be required to see a true effect. Although this seems plausible, supplementation of up to 3000 IU may be required to achieve such a large increase in vitamin D.

We can only hope that vitamin D will avoid the fate of folic acid [8,9] or vitamin E [10], which both held promise for the prevention of cardiovascular events based on data from observational studies but have been disappointing when tested in large-scale randomized controlled trials. To prove the benefit of vitamin D, a randomized controlled trial must be conducted with adequate supplementation among those who are 25(OH)D-deficient at baseline. Although the threshold for recommending vitamin D supplementation is already low because of its proven benefit for bone health, clear recommendations for vitamin D for the prevention of cardiovascular events will have to wait until more evidence becomes available.

Applications for Clinical Practice

Deficient 25(OH)D levels are associated with nonfatal MI and fatal CHD in men. Additional studies must be conducted to establish the clear role of supplementation for the prevention of cardiovascular events as well as how aggressive supplementation must be.

—Review by Jason P. Block, MD, MPH

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