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See related article, "Nephrin Deficiency Activates NF-κB and Promotes Glomerular Injury," on pages 1733–1743.

Low Calcidiol Levels and Coronary Artery Calcification: True, True, and Related?

Michal L. Melamed* and Ravi Thadhani†

*Departments of Medicine and Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York; and †Department of Medicine and Renal Unit, Massachusetts General Hospital, Boston, Massachusetts

J Am Soc Nephrol 20: 1663–1665, 2009.
doi: 10.1681/ASN.2009060610

There is increasing interest in the role of vitamin D in health and disease. From early articles showing associations between use of activated vitamin D and improved survival on dialysis[1] to more recent analyses showing that low 25-hydroxyvitamin D (calcidiol) and 1,25-dihydroxyvitamin D (calcitriol) levels are associated with mortality in dialysis patients,[2] the observational findings have been, for the most part, consistent. The associations between calcitriol use and survival have been extended to the predialysis chronic kidney disease (CKD) population,[3] as have associations between low calcidiol levels and mortality.[4] It is true that patients with renal disease represent an extreme population with profound deficiencies of both calcidiol and calcitriol. Low calcidiol levels associate with all-cause mortality in the general population.[5] The elevated mortality risk is perhaps due to an increased hazard for cardiovascular events. Low calcidiol levels link with incident cardiovascular disease (CVD)[6] and myocardial infarctions.[7] Studies of vitamin D deficiency and outcomes in the general population require larger sample sizes than studies of patients with renal disease because less profound deficiency is found in the former population.

The mechanisms underlying the benefits of adequate levels of vitamin D have not been fully elucidated. Low calcidiol levels associate with diabetes[8] and hypertension[9] and therefore may link to CVD by predisposing people with vitamin D deficiency to two diseases that place them at high risk. Vitamin D regulates the renin-angiotensin system[10] and may exert cardioprotection through this action. One of these effects may be protection against left ventricular hypertrophy. Activated vitamin D therapy prevents the progression of cardiac hypertrophy in the Dahl salt-sensitive rat model of heart failure.[11] The effect of calcitriol on cardiac structure and function has also been noted by other studies.[12,13]

Another area where vitamin D may play a role is in vascular calcification. One of the earliest models of atherosclerosis was an animal fed a high-cholesterol and high–vitamin D diet. These rats were fed 1.8 million U/kg vitamin D_2 and developed aortic atherosclerosis.[14] Recent experiments by Hruska and colleagues[15] showed that high dosages of calcitriol led to aortic calcification in a mouse model of CKD; however, low-dosage calcitriol, at dosages sufficient to treat secondary hyperparathyroidism, were protective against calcification. Thus, there may be an optimal level of activated vitamin D that is neither too high nor too low.

Human studies evaluating an association between vitamin D levels and coronary artery calcification (CAC) have shown conflicting results. An analysis of 650 Amish individuals did not find an association between calcidiol levels and prevalent CAC.[16] An analysis of 173 individuals at high risk for coronary artery disease found an inverse correlation between calcitriol levels and vascular calcification.[17] An analysis of 61 children on dialysis revealed that both high and low calcitriol levels associate with higher calcification scores.[18] This latter study potentially suggests an optimal level of vitamin D exists that is neither too high nor too low.

In this issue of *JASN*, de Boer *et al.*[19] report an analysis from the Multi-Ethnic Study of Atherosclerosis (MESA) suggesting

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Ravi Thadhani, Bullfinch 127, Massachusetts General Hospital, Boston, MA 02114. Phone: 617-724-1207; Fax: 617-726-2340; E-mail: thadhani.r@mgh.harvard.edu

that low calcidiol levels associate with subsequent development of CAC. In this well-analyzed study of 647 participants (mean age 64.0 yr; 35% white, 31% black, 13% Chinese, and 21% Hispanic; 21% with estimated GFR <60 ml/min per 1.73 m^2; 29% with calcidiol levels <15 ng/ml; all free from CAC at baseline), 135 participants developed incident CAC during 3 yr of follow-up. Low calcidiol levels were independently associated with a higher risk for developing CAC. Comparing those with calcidiol levels <15 ng/ml to those with levels ≥ 15 ng/ml, the risk was 1.38 (95% confidence interval [CI] 0.95 to 1.99) for developing incident CAC, but for each 10 ng/ml lower calcidiol level, the risk was 1.23 (95% CI 1.00 to 1.52; $P = 0.049$). Interestingly, the authors did not find an association between high calcidiol levels and CAC, either because one does not exist, or possibly there were not enough participants with higher levels of calcidiol. The association and the magnitude of the effect of low calcidiol levels and risk for CAC also did not seem as strong as those found for other cardiovascular risk factors in MESA.[20] For example, the multivariable adjusted relative risk for incident CAC for those with untreated diabetes was 1.49 (95% CI 1.06 to 1.79; $P = 0.02$) and among men was 1.72 (95% CI 1.42 to 2.09; $P < 0.001$).[20]

Strengths of this study include a well-characterized study population, free of clinical CVD at baseline but not free of subclinical CVD, such as CAC. An additional strength is the temporality of the association: Participants with low calcidiol levels at baseline subsequently developed CAC. Whereas most previous studies linking vitamin D and vascular calcification used a cross-sectional design, the study by de Boer *et al.*[19] is unique because of its prospective data. A few potential limitations of the study include that, in secondary analyses, calcidiol levels did not associate with the progression of plaque or severity of plaque. In other analyses of MESA, cardiovascular risk factors including age, male gender, white race, body mass index, elevated BP, and diabetes all were independently associated with progression of CAC.[20] Like most studies using rich databases, multiple comparisons without adjustment for statistically significant results are made in this analysis.

It is true that CACs associate with coronary events[21]; however, to be an ideal surrogate end point, regression of CAC needs association with a lowering of coronary events. This step has not been proved. Notably, studies of sevelamer hydrochloride showed less progression of calcification compared with calcium-based binders, but no randomized clinical trial showed a survival benefit to sevelamer in intention-to-treat analyses[22]; therefore, although CAC associates with coronary events and is considered a measure of subclinical atherosclerosis, it is unclear whether regression or less progression of CAC links with improved outcomes. It may be that CAC is yet another critical cardiovascular risk factor, which, like diabetes and hypertension, is now related to low calcidiol levels.

What does this study mean for patients with CKD and ESRD? In patients with ESRD, coronary events are not likely the primary cause of CVD deaths; instead, sudden cardiac death from arrhythmias are probably the most common causes of death, as recently suggested by large clinical trials.[23] Potentially, CAC associates with calcification in other vascular beds, which then leads to poor vascular compliance, left ventricular hypertrophy, and arrhythmias with sudden cardiac death. Calcification may be a marker of overall CVD status, rather than a specific risk factor for a unique cardiac event. Consequently, vitamin D effects on vascular calcification may be another mechanism whereby activated vitamin D plays a protective role in CKD, where a profound deficiency of this important hormone is highly prevalent.

What does this study mean for the general population? These observational studies, like those published in the past, require confirmation by trials. Although the general population does not have as profound a vitamin D deficiency as those with CKD, a significant portion of the population in the United States have calcidiol levels <15 ng/ml.[24] This deficiency may put them at risk for the development of diabetes, hypertension, and possibly CAC. It is important to remember that high levels of vitamin D may also have deleterious effects; therefore, exuberant use of this therapy should not be encouraged. Randomized clinical trials of vitamin D supplementation are needed to evaluate whether the associations seen in these observational studies will translate into true effects or just represent confounding as in many classic examples. These studies may be better performed in patients with CKD, in whom there is more profound deficiency and thus a larger effect (if one exists) may be seen. The challenge, of course, is when we will obtain these definitive results.

ACKNOWLEDGMENTS

M.L.M. is supported by K23 DK078774 from the National Institutes of Health and by an American Heart Association Clinically Applied Research Award; R.T. is supported by grant HL093954 from the National Institutes of Health.

DISCLOSURES

M.L.M. has received honoraria from Medscape and the American Society of Nephrology; R.T. has received grant support from Abbott Laboratories and speaking honoraria from Abbott and Genzyme.

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