Editorial

Is Coronary Artery Calcification at the Intersection of Vitamin D and Coronary Artery Disease?

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Cardiovascular disease is the leading cause of death among men and women in developed countries.[1] Most of this premature mortality occurs in a subgroup of the population that is prone to accelerated atherogenesis caused by genetic, lifestyle, and environmental factors, along with their interactions. Growing evidence suggests that vitamin D deficiency is associated with coronary artery disease (CAD) development.[2] However, mechanistic evidence supporting this association is lacking. Coronary artery calcification (CAC) is strongly associated with risk of vascular disease,[3,4] and several studies report an inverse relationship between levels of the active form of vitamin D and atherosclerotic calcification.[5] Therefore, it is important to understand if vitamin D metabolism influences degree of CAC; insights into this relationship would provide support for a role of vitamin D in the pathogenesis of CAD.

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In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Shen et al[6] present a well-designed candidate gene study to investigate the association of single-nucleotide polymorphisms (SNPs) in key genes involved in vitamin D metabolism with CAC. The CAC phenotype was quantified as the sum of the calcification scores in both left and right coronary arteries. The researchers selected 5 genes, cytochrome P450, family 2, subfamily R *(CYP2R1)*, cytochrome P450, family 27, subfamily B *(CYP27B1)*, cytochrome P450, family 24, subfamily A *(CYP24A1)*, vitamin D receptor *(VDR)*, Viatmin D-binding protein *(GC)*, known to be involved in vitamin D homeostasis.[6–8] In the discovery phase, they conducted the association analysis in samples from Amish families (N=697), with 39 genotyped SNPs from 4 available genes using a chip (HumanCVD BeadChip V2). Although no SNPs in the *CYP27B1*, *VDR*, or *GC* genes were associated with CAC score, 4 SNPs in the *CYP24A1* gene were nominally associated with CAC score ($P=0.008$ to $P=0.00003$) in the discovery phase. Then, these 4 SNPs were tested for replication in samples from the Genetic Epidemiology Network of Arteriopathy (N=916) and the Penn Coronary Artery Calcification (N=2061), 2 independent cohorts of European white ancestry (Figure). In the replication phase, 1 of these 4 SNPs, *rs2762939*, demonstrated evidence of an association with CAC in both the Genetic Epidemiology Network of Arteriopathy and the Penn Coronary Artery Calcification cohorts ($P=0.01$ and $P=0.007$, respectively). The subsequent meta-analysis of the data from these 3 populations yielded a probability value of 2.9×10^{-6} for *rs2762939*. However, in further analysis, they could not find any association between circulating levels of 25-hydroxy-vitamin D (25[OH]D) levels and this SNP in relatively small populations.

The results of the study conducted by Shen et al raise the possibility of the role of vitamin D homeostasis in CAC development. The *CYP24A1* gene product is central to vitamin D regulation because it degrades the active form of vitamin D, 1,25-dihydroxy-vitamin D ($1,25[OH]_2D$). Despite the fact that previous transgenic studies have revealed the role of the *CYP24A1* gene on stability plasma level of $1,25(OH)_2D$ and 25(OH)D,[9] the current study did not establish any association between *rs2762939* and 25(OH)D levels. In addition, $1,25(OH)_2D$ levels were not available for researchers to assess this possible association. It remains possible that the identified SNP may influence $1,25(OH)_2D$ levels and, consequently, CAC, without affecting vitamin D stores, as reflected by 25(OH)D levels. Therefore, it is important that the association between *rs2762939*, 25(OH)D, $1,25(OH)_2D$, and other coronary disease outcomes be clarified in adequately powered consortia designed to identify the genetic determinants of vitamin D levels or CAD.[10] Further-

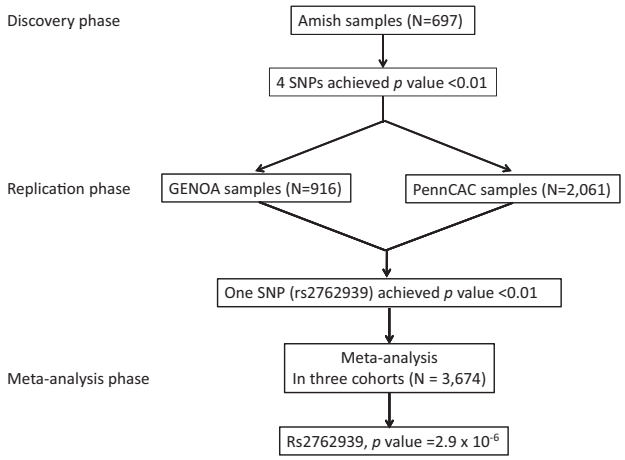

Figure. The strategy used by Shen and colleagues[6] to investigate whether DNA sequence variants in the *candidate* genes in vitamin D metabolism contribute to Coronary Artery Calcification.

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(*Arterioscler Thromb Vasc Biol*. 2010;30:2329-2330.)

***Arterioscler Thromb Vasc Biol* is available at http://atvb.ahajournals.org**
DOI: 10.1161/ATVBAHA.110.216218

more, it will be worthwhile to investigate whether this SNP affects the transcription and protein product levels of the genes involved in the maintenance of $1,25(OH)_2D$ and 25(OH)D levels.

This finding raises interesting questions about the direct role of vitamin D in the progression or initiation of atherosclerosis. Other research has discovered that vitamin D lowers the activity of the inflammatory activator nuclear factor κB, inhibiting foam cell formation and suppressing macrophage cholesterol uptake in patients with type 2 diabetes mellitus.[11,12] On the other hand, vitamin D levels are correlated with other CAD risk factors, such as hypertension, hyperlipidemia, and diabetes.[13–17] Therefore, the described association may occur directly through vitamin D metabolism or indirectly through other pathways, regardless of their effect on 25(OH)D, by influencing known risk factors for cardiovascular disease (ie, hypertension, diabetes, and inflammation).

This study suggests a role for vitamin D homeostasis in CAC and provides an important signpost on the road toward understanding the role of calcium and vitamin D metabolism in risk of CAD.

Disclosures

None.

References

1. Castelli WP. Epidemiology of coronary heart disease: The framingham study. *Am J Med*. 1984;76:4–12.
2. Levin A, Li YC. Vitamin d and its analogues: Do they protect against cardiovascular disease in patients with kidney disease? *Kidney Int*. 2005; 68:1973–1981.
3. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with framingham score for risk prediction in asymptomatic individuals. *JAMA*. 2004;291:210–215.
4. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: Mean three-year outcomes in the prospective army coronary calcium (pacc) project. *Journal of the American College of Cardiology*. 2005;46:807–814.
5. Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, Demer LL. Active serum vitamin d levels are inversely correlated with coronary calcification. *Circulation*. 1997;96:1755–1760.
6. Shen H, Bielak LF, Ferguson JF, Streeten EA, Yerges-Armstrong LM, Liu J, Post W, O'Connell JR, Hixson JE, Kardia SL, Sun YV, Jhun MA, Wang X, Mehta NN, Li M, Koller DL, Hakonarson H, Keating BJ, Rader DJ, Shuldiner AR, Peyser PA, Reilly MP, Mitchell BD. Association of the vitamin d metabolism gene cyp24a1 with coronary artery calcification. *Arterioscler Thromb Vasc Biol*. 2010.
7. Tashiro K, Abe T, Oue N, Yasui W, Ryoji M. Characterization of vitamin d-mediated induction of the cyp 24 transcription. *Mol Cell Endocrinol*. 2004;226:27–32.
8. Ponchon G, Kennan AL, DeLuca HF. "Activation" Of vitamin d by the liver. *J Clin Invest*. 1969;48:2032–2037.
9. Takeyama K, Kitanaka S, Sato T, Kobori M, Yanagisawa J, Kato S. 25-hydroxyvitamin d3 1alpha-hydroxylase and vitamin d synthesis. *Science*. 1997;277:1827–1830.
10. Kasuga H, Hosogane N, Matsuoka K, Mori I, Sakura Y, Shimakawa K, Shinki T, Suda T, Taketomi S. Characterization of transgenic rats constitutively expressing vitamin d-24-hydroxylase gene. *Biochem Biophys Res Commun*. 2002;297:1332–1338.
11. Psaty BM, O'Donnell CJ, Gudnason V, Lunetta KL, Folsom AR, Rotter JI, Uitterlinden AG, Harris TB, Witteman JC, Boerwinkle E. Cohorts for heart and aging research in genomic epidemiology (charge) consortium: Design of prospective meta-analyses of genome-wide association studies from 5 cohorts. *Circ Cardiovasc Genet*. 2009;2:73–80.
12. Oh J, Weng S, Felton SK, Bhandare S, Riek A, Butler B, Proctor BM, Petty M, Chen Z, Schechtman KB, Bernal-Mizrachi L, Bernal-Mizrachi C. 1,25(oh)2 vitamin d inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. *Circulation*. 2009;120:687–698.
13. Cohen-Lahav M, Shany S, Tobvin D, Chaimovitz C, Douvdevani A. Vitamin d decreases nfkappab activity by increasing ikappabalpha levels. *Nephrol Dial Transplant*. 2006;21:889–897.
14. Sepulveda JL, Mehta JL. C-reactive protein and cardiovascular disease: A critical appraisal. *Curr Opin Cardiol*. 2005;20:407–416.
15. McCarty MF. Secondary hyperparathyroidism promotes the acute phase response – a rationale for supplemental vitamin d in prevention of vascular events in the elderly. *Med Hypotheses*. 2005;64:1022–1026.
16. Holick MF. High prevalence of vitamin d inadequacy and implications for health. *Mayo Clin Proc*. 2006;81:353–373.
17. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-dihydroxyvitamin d(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest*. 2002;110:229–238.
18. Forman JP, Curhan GC, Taylor EN. Plasma 25-hydroxyvitamin d levels and risk of incident hypertension among young women. *Hypertension*. 2008;52:828–832.

KEY WORDS: atherosclerosis ■ calcification ■ calcium ■ coronary artery disease ■ vitamin D