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

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Coronary artery calcification (CAC) is strongly associated with risk of vascular disease, and several studies report an inverse relationship between levels of the active form of vitamin D and atherosclerotic calcification. 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.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Shen et al 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), vitamin D-binding protein (GC), known to be involved in vitamin D homeostasis. 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, 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. Further-

Figure. The strategy used by Shen and colleagues to investigate whether DNA sequence variants in the candidate genes in vitamin D metabolism contribute to Coronary Artery Calcification.
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 2B, inhibiting foam cell formation and suppressing macrophage cholesterol uptake in patients with type 2 diabetes mellitus.\textsuperscript{11,12} On the other hand, vitamin D levels are correlated with other CAD risk factors, such as hypertension, hyperlipidemia, and diabetes.\textsuperscript{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


Key Words: atherosclerosis ■ calcification ■ calcium ■ coronary artery disease ■ vitamin D