Editorial

Vitamin D and Risk of Cardiovascular Disease

Shoaib Afzal, Børge G. Nordestgaard

Observational studies have mostly found a strong association of low plasma 25-hydroxyvitamin D (25(OH)D), usually used to measure vitamin D status, with increased risk of coronary heart disease, stroke, and cardiovascular death.[1–3] However, recent Mendelian randomization studies and randomized intervention trials do not support a causal association of 25(OH)D or vitamin D supplementation with cardiovascular disease.[4–8] This discrepancy has been ascribed to failures to account either for confounding or reverse causation in observational studies or for the nonlinear relationships in genetic studies and inappropriate recruiting of vitamin D replete individuals to vitamin D supplementation trials.

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In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Qi et al[9] present a comprehensive report on the association of 25(OH)D and other biomarkers of vitamin D status on coronary heart disease. Using the Nurses' Health Study in a nested case–control design with 382 cases and 575 controls and 20-year follow-up, they show independent associations of VDBP (vitamin D–binding protein) with coronary heart disease and an interaction of 25(OH)D with parathyroid hormone on risk of coronary heart disease (Figure). However, 25(OH)D was not independently associated with coronary heart disease. In essence, this report claims that reality may be more complex than claiming that low 25(OH)D is a risk factor for coronary disease (Figure). The main limitation of these findings is that this is an observational study that cannot escape residual confounding; therefore, causal claims cannot be substantiated beyond reference to biological plausibility. Other limitations include the modest sample size and the relatively high mean levels of 25(OH)D in the population studied. In addition, there are no immediate consequences for clinical practice. Nevertheless, this study also underlines the strengths of observational studies: the ease, with which complex hypotheses can be tested, and generation of new testable hypotheses that may be evaluated in superior designs to improve clinical practice.

This study[9] adds to the growing literature indicating that biomarkers of vitamin D status beyond 25(OH)D may have an independent role in cardiovascular disease. Previous studies have shown that VDBP is a carrier for actin, and VDBP may be important in regulation of inflammatory responses. Inflammation has been shown to be important in causing coronary heart disease,[10] and in experimental studies, actin metabolism has also been linked to cardiovascular disease.[11,12] Such data indicate that VDBP could be a confounder in the association of 25(OH)D with coronary heart disease. However, several large studies, using genetic variants in *VDBP* that are associated with VDBP levels,[13] have failed to show an association with cardiovascular end points, decreasing the enthusiasm for pursuing this as a potential therapeutic target.[14–17] Furthermore, genetic variants associated with VDBP levels have been present on arrays (metabochip and exome chip) used in large consortia investigating cardiovascular disease but have not shown up as a hit in any of them. In contrast, the interaction of 25(OH)D with parathyroid hormone has been sparsely investigated. Despite the number of statistical comparisons presented in the modestly sized case–control study by Qi et al, we think, as the authors also state, that this question deserves further investigation because the present results cannot be interpreted as being decisive.

In conclusion, the study by Qi et al highlights that other biomarkers of vitamin D status could be independently associated with risk of coronary heart disease and that there could be potential interactions of the biomarkers with regard to risk of coronary heart disease. Further studies are needed to investigate these hypotheses and any potential consequences for clinical practice. Most importantly, we are all awaiting the randomized intervention of vitamin D supplementation to be published in the near future (eg, ViDA [The Vitamin D Assessment], CAPS [Clinical Trial of Vitamin D3 to Reduce Cancer Risk in Postmenopausal Women], VITAL [Vitamin D

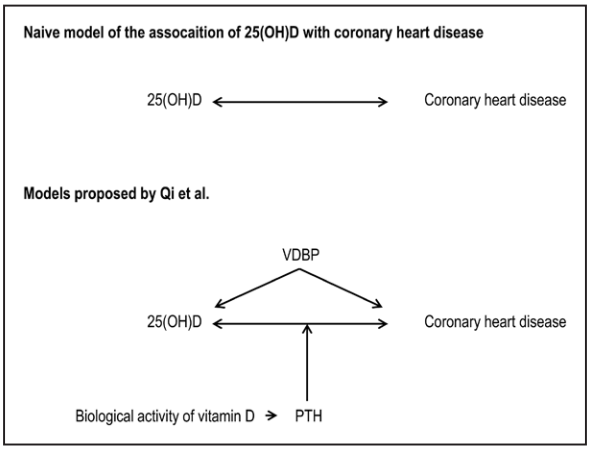

Figure. Proposed models for the association of biomarkers of vitamin D status with risk of coronary disease. 25(OH)D indicates 25-hydroxyvitamin D; PTH, parathyroid hormone; and VDBP, vitamin D–binding protein.

From the Department of Clinical Biochemistry and The Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Denmark (S.A., B.G.N.); Faculty of Health and Medical Sciences, University of Copenhagen, Denmark (B.G.N.); and The Copenhagen City Heart Study, Frederiksberg Hospital, Copenhagen University Hospital, Denmark (B.G.N.).

Correspondence to Shoaib Afzal, MD, PhD, Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark. E-mail shoaib.afzal@regionh.dk

(*Arterioscler Thromb Vasc Biol*. 2017;37:1981-1982. DOI: 10.1161/ATVBAHA.117.310204.)

***Arterioscler Thromb Vasc Biol* is available at http://atvb.ahajournals.org**
DOI: 10.1161/ATVBAHA.117.310204

and Omega-3 Trial], DO-HEALTH [Vitamin D3 - Omega3 - Home Exercise - Healthy Ageing and Longevity Trial], and FIND [Finnish Vitamin D Trial]).[8,18] These randomized trials will provide us with definitive answers as to whether vitamin D supplementation will reduce cardiovascular disease or not and whether vitamin D is causally related to cardiovascular disease.

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KEY WORDS: Editorials ■ cardiovascular disease ■ parathyroid hormone ■ vitamin D ■ vitamin D-binding protein

Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Arterioscler Thromb Vasc Biol. 2017;37:1981-1982
doi: 10.1161/ATVBAHA.117.310204
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1079-5642. Online ISSN: 1524-4636