# Have We Been Measuring the Wrong Form of Vitamin D?

## Vitamin D as a Prognostic Biomarker for Coronary Artery Disease Mortality

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The role of vitamin D in coronary artery disease (CAD) has been under intense debate, with inconsistent results regarding its potential prognostic value and therapeutic role. Numerous studies have indicated that vitamin D deficiency is linked to morbidity and mortality,[1] purporting a role in inflammation, impaired endothelial function, and vascular stiffness, as well as an association with worse blood glucose, blood pressure, and lipid control.[2,3] Nonetheless, various studies have failed to show a benefit of vitamin D supplementation on CAD risk or on markers of inflammation, endothelial function, hypertension, hyperlipidemia, or diabetes mellitus.[4] Thus, this conundrum is highlighted by the fact that significant predictive correlations between low vitamin D levels and CAD risk do not translate into clinical therapeutic relevance and may be just an epiphenomenon.[3] However, it is important to note that there are significant discrepancies in study results depending on what form of vitamin D was measured and which antibodies were used for the assay.[5,6] Therefore, is it possible that the discrepancy in study findings is a result of measuring the wrong form of vitamin D or using the wrong assay?

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In this edition of *Circulation Research*, Yu et al[7] targets this critical question by exploring the associations between all-cause and cardiovascular mortality and serum total, bioavailable, and free 25-hydroxyvitamin D levels in patients with CAD. Accordingly, 1387 patients with CAD were assessed for these levels at baseline and ≈ 6.7 years later. Ultraperformance liquid chromatography-tandem mass spectrometry was used to measure total 25-hydroxyvitamin D (sum of D2 and D3). DBP (vitamin D-binding protein) was measured using a polyclonal, instead of the more commonly used monoclonal antibody via ELISA. Free 25-hydroxyvitamin D was measured using a 2-step ELISA kit, and bioavailable 25-hydroxyvitamin D was calculated using total 25-hydroxyvitamin D, DBP, albumin levels, and affinity constants for albumin and DBP isoforms. Interestingly, the authors found that lower serum bioavailable and free 25-hydroxyvitamin D levels correlated with increased risk of all-cause and cardiovascular mortality, whereas total levels had no correlation to mortality risks. Notably, most studies report total 25-hydroxyvitamin D levels, and there is variability in the assays used, perhaps accounting for the lack of consensus in the field. Here, Yu et al[7] suggests a paradigm shift away from traditional vitamin D measurements. Albeit, we must caution the role ethnicity may have played in this study, as all participating patients were Chinese—a population with relatively lower levels of CAD mortality compared with the Western population.[8] Nevertheless, this study leaves us enticed to wonder how the measurement of bioavailable and free 25-hydroxyvitamin D in prior clinical trials would have affected the results. Furthermore, does changing the specific forms of vitamin D levels that are measured translate into meaningful clinical therapeutic advancements?

The literature unequivocally demonstrates the link between low vitamin D levels and cardiovascular diseases.[1,2] Delving further into the literature highlights that vitamin D deficiency is found in a multitude of diseases,[9,10] as well as is markedly evident in otherwise healthy subjects.[11] How is vitamin D deficiency implicated so widely? If that is the case, why does not vitamin D supplementation seem to yield attainable clinical benefits? Yu et al[7] makes an important contribution to the field by demonstrating that total 25-hydroxyvitamin D—a parameter that has been commonly used to assess vitamin D body stores—is perhaps not what we should be measuring, but rather bioavailable and free 25-hydroxyvitamin D.

Another important factor when discussing vitamin D levels is the effect race and ethnicity plays in measurements and guidelines for what dictates deficiency. Weishaar et al[12] performed a wide-scale analysis on the effect of body weight and race/ethnicity on vitamin D levels, showing that both parameters significantly affected its measurement levels. Specifically, people with darker skin colors or heavier body weights had a higher probability of vitamin D deficiency, suggesting that using a universal guideline for diagnosing deficiency may be inaccurate. In a cross-sectional analysis, Gutiérrez et al[13] illustrated that the relationships between 25-hydroxyvitamin D, bone mineral density, and parathyroid hormone levels vastly differed between Blacks, Mexican-Americans, and Whites.

In summary, despite the evidence linking CAD and vitamin D deficiency, vitamin D supplementation trials have not yielded convincing clinical benefits.[14,15] Ultimately, we must ask ourselves, first, are we correctly defining what normal vitamin D levels are in different patient populations, and second, are we chasing after simply discerning a biomarker for



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increased CAD risk or is vitamin D actually a crucial part in the pathogenesis?

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## Disclosures

None.

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