EDITORIAL COMMENT

Vitamin D Deficiency and Heart Failure Risk
Not so Black and White?*

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In the past decade, interest in vitamin D has blossomed, driven in large part by epidemiologic studies linking low vitamin D status with a variety of adverse health outcomes. The association of vitamin D deficiency with cardiovascular disease has generated particular attention, and for good reason, because the public health implications of a new, easily modifiable risk factor for cardiovascular disease are enormous. Because vitamin D deficiency is more common among blacks and individuals in developed countries, it has even been speculated that vitamin D supplementation could address some of the well-documented racial/ethnic and geographic disparities in cardiovascular risk.

Studies that have related vitamin D status to specific cardiovascular endpoints have largely focused on coronary heart disease (1,2). There are fewer reports addressing vitamin D deficiency and heart failure risk, although several studies have suggested an association (3-5). The biological rationale for investigating the relation between vitamin D and heart failure stems from preclinical studies suggesting an important role for vitamin D in cardiovascular homeostasis. Vitamin D is a negative regulator of the renin-angiotensin-aldosterone system, and mice globally deficient in the vitamin D receptor display elevated levels of circulating renin, higher blood pressure, and ventricular hypertrophy (6,7). Vitamin D receptor is also present on mouse and human cardiomyocytes, and mice with cardiac-specific deletion of vitamin D receptor demonstrate cardiac hypertrophy, indicating that vitamin D has direct effects on cardiomyocytes (8).

In their paper in this issue of JACC: Heart Failure, Lutsey et al. (9) from the ARIC (Atherosclerosis Risk in Communities) study examined whether low serum 25-hydroxyvitamin D [25(OH)D] is associated with incident heart failure in a multiethnic epidemiologic cohort. Among 12,215 individuals (24% black) initially free of heart failure, low total serum 25(OH)D was associated with incident heart failure over a median follow-up time of 18 years in whites but not blacks. In whites, the risk for incident heart failure for those in the lowest quintile of 25(OH)D was nearly twice that of those in the highest quintile (referent), after adjusting for age and sex. The hazard ratio was 1.27 (95% confidence interval: 1.04 to 1.55) after full adjustment for cardiovascular risk factors. As in prior observational studies, the risk seemed to be considerably higher at 25(OH)D levels below 20 ng/ml (2). No association between 25(OH)D levels and incident heart failure was seen in black individuals.

The Lutsey study (9) has many strengths, including its large sample size and use of a well-characterized, biracial cohort. Why would the association between 25(OH)D levels and heart failure differ in white versus black individuals? Black individuals generally have much lower 25(OH)D concentrations than whites, an observation that has typically been attributed to differences in skin darkness and ultraviolet light penetration. It is becoming increasingly apparent, however, that low

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absolute 25(OH)D levels in black individuals may overstate the degree of deficiency. One reason is that black individuals also tend to have lower levels of vitamin D binding protein (DBP). Up to 90% of 25(OH)D is bound to DBP and unavailable for biological activity (10). Because lower DBP levels should permit greater bioavailability of vitamin D at target organs, levels of 25(OH)D that cause physiologic “deficiency” in white individuals may not do so in black individuals.

One explanation for the lower levels of DBP in black individuals is genetic variation at GC, the gene that encodes DBP (11). The G allele of the GC single-nucleotide polymorphism rs7041, which is more common in individuals of European ancestry, results in a substitution of aspartic acid with glutamic acid at amino acid 432 (p.Asp432Glu), and is known to increase levels of DBP (12). Thus, the authors further analyzed whether the association between vitamin D status and heart failure varied by this genotype. They found that the association between low vitamin D and heart failure was particularly prominent among participants homozygous for the rs7041 G allele. In this group, those in the lowest quintile of 25(OH)D had 1.67 (95% confidence interval: 1.15 to 2.42) times greater risk of incident heart failure after multivariable adjustment. There was no association between 25(OH)D and incident heart failure among TG and TT genotype subjects.

These observations raise the question whether the race interaction (e.g., the greater association between vitamin D and heart failure in whites) is attributable to the fact that white individuals are much more likely to have DBP-raising alleles in GC. Interestingly, black individuals with at least one rs7041 G allele did exhibit a stronger association between vitamin D status and heart failure risk, although confidence intervals were wide in this subgroup analysis. Conversely, white individuals who lacked the G allele seemed to have no association between vitamin D status and heart failure risk. These observations are intriguing, although larger studies are needed to definitively establish the role of genetic variation in GC (e.g., in rs7041 and other single-nucleotide polymorphisms) in the race interaction. Moreover, although common genetic variation accounts for a large proportion of the variation in DBP levels (12), environmental factors also can contribute (13). In this regard, it would have been useful to have actual DBP concentrations assessed in this cohort, a limitation that the authors acknowledge.

The findings of Lutsey et al. (9) provide persuasive evidence of association between vitamin D status and incident heart failure in white individuals. Although similar associations have been demonstrated for other cardiovascular endpoints, heart failure is an important cause of morbidity and mortality, and is prevalent in populations that also happen to have vitamin D deficiency, including those with advanced age, obesity, and insulin resistance. Importantly, however, the study leaves open the question of whether the association with heart failure is causal. Despite the experimental and observational data suggesting that low vitamin D status could promote cardiac dysfunction, corroborating evidence from studies with vitamin D supplementation is lacking (14,15). For other, nonskeletal outcomes, clinical trials of vitamin D supplementation have failed to confirm hypotheses raised by observational studies. For instance, a large body of experimental and observational evidence suggests a link between vitamin D deficiency and blood pressure, but prospective trials have generally shown no effect of vitamin D supplementation on blood pressure (16-18).

Whether or not the association of vitamin D deficiency with heart failure is causal, the subgroup results contribute to an emerging understanding of how race interacts with vitamin D status. It has been hypothesized that mechanisms to increase the efficiency of vitamin D transport or metabolism can represent adaptations to low vitamin D stores. For example, compared with whites, blacks tend to have higher circulating 1,25(OH)2D relative to 25(OH)D (19). Reduced circulating DBP may represent a similar adaptation to low total 25(OH)D.

As clinicians continue to explore the relationship between vitamin D status and cardiovascular diseases, such as heart failure, it seems increasingly clear that race will be an important consideration. Circulating 25(OH)D levels, an important measurement in clinical practice, may be a poorer biomarker of vitamin D status in blacks than in whites. Whether DBP, genotype, or downstream metabolites of vitamin D should be measured clinically in black individuals to aid the assessment of vitamin D status is a question that warrants further investigation.

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