Response to Letter by Tsuda Regarding Article, “Vitamin D Deficiency Is Associated With Subclinical Carotid Atherosclerosis: The Northern Manhattan Study”

Response:

We are grateful to Dr Tsuda for his interest in our work demonstrating an association between low 25-hydroxyvitamin D (25OHD) levels and thicker carotid plaque and carotid intima-media thickness. Raising the possibility that low bone mineral density (BMD), hypertension, stroke, and vitamin D deficiency may be related, he questions whether 25OHD levels are associated with blood pressure or BMD in our study. Although BMD was not measured in this cohort, low 25OHD levels are known to be associated with lower BMD and higher fracture rates.1 We found no association between 25OHD and hypertension. Those with and without hypertension had similar 25OHD levels (mean±SD 22.3±10 vs 22.3±11 ng/mL; P=1.0). Likewise, 25OHD deficiency (<20 ng/mL) was not associated with the presence of hypertension (odds ratio [OR], 0.81; 95% confidence interval [CI], 0.5–1.4). There was no correlation between 25OHD and systolic or diastolic blood pressure (r=0.09; P=0.89). In those with carotid plaque, there was also no association between 25OHD levels and hypertension (normotensive 23.8±8 vs hypertensive 23.2±11 ng/mL; P=1.0; OR, 0.54; 95% CI, 0.24–1.2), systolic blood pressure (r=0.05; P=0.59), or diastolic blood pressure (r=−0.09; P=0.35).

The relationship between mineral metabolism and cardiovascular disease is complex and our understanding continues to evolve. Numerous studies reveal an inverse relationship between 25OHD levels and cardiovascular events/mortality independent of traditional cardiovascular risk factors.2 Although in vitro and animal data suggest that the cardiovascular effects of 25OHD deficiency are attributable to activation of the renin-angiotensin system and inflammatory changes that may lead to hypertension, cardiac hypertrophy, and atherogenesis, human data are sparse. Furthermore, the intricate inter-regulation of calcium, phosphorus, vitamin D metabolites, and parathyroid hormone necessitates considering the roles of other indices of mineral metabolism in determining the cardiovascular effect of 25OHD. Despite the null results reported here, limited data support a modest decline in blood pressure with vitamin D treatment.3

Dr Tsuda also refers to a body of literature supporting a relationship between osteoporosis and increased risk of cardiovascular disease, but whether this association is causal has not been definitively demonstrated. Cardiovascular disease could directly affect bone by decreasing peripheral blood supply, thereby suppressing bone cell function. Alternatively, atherosclerosis might limit physical activity, leading to bone loss. Confounding could also explain the association. Advanced age, smoking, inactivity, renal disease, diabetes, menopause, homocysteinuria, and inflammation are risk factors for both cardiovascular disease and osteoporosis. Although it is plausible that vitamin D deficiency contributes to both osteoporosis and cardiovascular disease, data suggest that the relationship between cardiovascular disease and mineral metabolism is multifactorial. Vascular calcification is a highly regulated process resembling osteogenesis. A shared origin for both cardiovascular disease and osteoporosis can be observed in osteoprotegerin-deficient mice that develop both osteoporosis and aortic calcification,4 as well as in individuals with low-density lipoprotein receptor-related protein 6 mutations who develop early atherosclerosis and osteoporosis.5

Given the high prevalence of vitamin D deficiency and the vast burden of cardiovascular disease, it is appealing to consider vitamin D deficiency as a modifiable cardiovascular risk factor. Our report adds to the existing data suggesting a link between vitamin D and cardiovascular disease. However, future studies must investigate the pathophysiology as well as the causality of the association between vitamin D and cardiovascular health. Finally, large randomized controlled trials examining the effect of vitamin D treatment on cardiovascular health are vital before recommending treatment for this purpose.

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Disclosures

None.

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