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# Vitamin D for the prevention of stroke incidence and disability: Promising but too early for prime-time

**Erin D. Michos, MD, MHS**[1] and **Rebecca F. Gottesman, MD, PhD**[2]

Erin D. Michos: edonnell@jhmi.edu

[1]Department of Medicine (Cardiology), Johns Hopkins University School of Medicine, Baltimore, MD, USA

[2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Vitamin D is a neurosteroid, with vitamin D receptors widely expressed in the brain, both in neuronal and glial cells. Genes encoding enzymes for both the metabolism and degradation of activated vitamin D [1,25(OH)2D or calcitriol] are also found in the brain.[1] Vitamin D may play a role in neuroprotection, perhaps through detoxification pathways, inhibition of inducible nitric oxide synthase, antioxidation/anti-inflammatory mechanisms, neuronal calcium regulation, or enhanced nerve conduction.[1] Vitamin D may also prevent vascular injury through lowering blood pressure, inhibiting the renin-angiotensin-aldosterone system, and inhibiting atherogenesis.[2]

These mechanistic hypotheses are supported by epidemiologic literature demonstrating an association between vitamin D deficiency and both neurodegenerative and vascular dementias. Low circulating 25(OH)D levels [the best biomarker of vitamin D status] have been associated with cognitive decline in the elderly[3], and one cross-sectional study found lower 25(OH)D levels associated with more white matter hyperintensities and large vessel infarcts.[4]

Low 25(OH)D has also been associated with incident cerebrovascular disease. In 6,219 participants in the Mini-Finland Health Survey, individuals with 25(OH)D levels in the highest quintile were at lower risk of fatal stroke over 27 years than were those in the lowest quintile [HR:0.48 (95% CI: 0.31–0.75)].[5] A recent meta-analysis which pooled the results of 7 prospective observational studies found that low 25(OH)D levels were associated with increased risk of incident stroke [RR 1.52 (95% CI 1.20–1.85].[6]

In this journal issue, Daubail et al show a novel association between low 25(OH)D levels and acute ischemic stroke severity, using the National Institutes of Health Stroke Scale, as well as greater early functional impairment using the modified Rankin scale (mRS).[7] These suggest that low 25(OH)D levels, a treatable risk factor, might be targeted for the reduction of disability among stroke sufferers.

This study, however, must be viewed in the context of several important limitations. As with all observational studies, causation cannot be determined. Although age and certain cardiovascular risk factors such as diabetes and smoking were included in their multivariate models, residual confounding may still explain the associations seen. Individuals with reduced functional ability prior to the stroke are less likely to be doing outdoor physical

Corresponding author: Erin D. Michos, MD, MHS, Assistant Professor of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine, Carnegie 568, 600 N. Wolfe Street, Baltimore, MD, 21287, USA, Office: 410-502-6813, Fax: 410-502-0231.

activity (i.e. resulting in lower 25(OH)D levels), and are more vulnerable to worse outcomes after the stroke. Thus, low 25(OH)D may just be a good surrogate marker for a poorer health status at baseline. In addition, the dichotomization of the mRS as the primary outcome allows only for crude associations between 25(OH)D category and functional status. Analyzing 25(OH)D levels over the full range of the mRS might provide more evidence for or against the importance of 25(OH)D levels in stroke severity.

This was also a small study, and of exclusively Caucasians; findings may not be applicable to other race/ethnicities with darker skin pigmentation who are most at risk for vitamin D deficiency and might benefit most from treatment. 25(OH)D levels were measured on admission and may not reflect lifetime vitamin D status. Vitamin D deficiency was defined at a severe threshold (<25.7 nmol/L or 10.3 ng/ml), and results may not necessarily be extended to milder forms of deficiency. The 2011 Institute of Medicine report suggested levels ≥20 ng/ml (50 nmol/L) may be sufficient for health.[8]

Despite the limitations of the observational design, the findings observed by Daubail et al are further reinforced by a recent experimental model of adult rats by Balden et al.[9] Vitamin D deficient rats subjected to acute middle cerebral artery occlusion had larger infarct size and worse post-infarct behavioral testing compared to control rats, and had dysregulation of their inflammatory response with reduced expression of neuroprotective growth factors such as IGF-1. However, in these animals, acute treatment with vitamin D did not improve stroke severity or performance.

In conclusion, the observational literature associating low 25(OH)D levels to incident stroke and the new findings by Daubail further linking vitamin D status to stroke severity and disability are enticing. This is bolstered by plausible biological mechanisms obtained through animal and experimental models, but randomized clinical trial data are lacking. Vitamin D deficiency is easy to screen for, and inexpensive treatment exists in the form of modest sunlight exposure and vitamin D supplementation. However randomized clinical trials of vitamin D supplementation designed to look at clinical stroke endpoints are needed before prevention guidelines for widespread screening and treatment can be implemented. Previously, the scientific community has been burned in the saga of hormone therapy, antioxidants, and folate/B vitamins where there was discordance between observational data and randomized clinical trials for the use of these therapies in cardiovascular disease prevention. Only time will tell whether vitamin D will live up to its hype.

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