

# Vitamin D and Cerebrovascular Disease

## EDITORIAL COMMENTARY

Vitamin D [25-Hydroxyvitamin D (25(OH) D)], is a secosteroid provitamin obtained by dermal synthesis following exposure to sun and through oral consumption from food and supplements. Though initially related to bone and mineral homeostasis, a diversified range of physiological roles of 25(OH) D has been documented over the years. Concurrently, a vast array of >100 human diseases have been linked to low circulating concentrations of 25(OH) D.<sup>[1]</sup> The intriguing but worrisome estimates of more than a half of global population with inadequate vitamin D status, suggest a vast potential for vitamin D-based interventions targeted at the prevention, and management of these diseases.<sup>[2]</sup>

In the present point-of-view article, the authors have presented an epidemiological as well as clinical perspective on the incidence, severity, and rehabilitation of stroke caused by vitamin D deficiency.<sup>[3]</sup> Although a decline in stroke mortality has been documented recently in developed nations because of the implementation of strict guidelines on risk factor management like hypertension,<sup>[4,5]</sup> the global burden of stroke continues to rise due to an increase in the developing countries.<sup>[4]</sup> The authors have presented an overall view on the association of vitamin D status with stroke risk; most of the evidence discussed is derived from reported observational prospective studies.<sup>[3]</sup> The authors have also given a run-through over the status of intervention studies; however, a few important reports could be included. To this end, we would like to refer to the recently published, randomized, placebo-controlled, VITAL trial, that reported no decrease in the incidence of cardiovascular events including stroke in the elderly, when the use of vitamin D supplements and marine omega-3 fatty acids were compared with placebo, during a mean follow-up of 5.3 years.<sup>[6]</sup> The trial concluded that the beneficial influences of vitamin D supplementation on stroke risk could only be limited to severely vitamin D deficient individuals. The finding raises concerns on the implementation of vitamin D supplementation for the prevention of stroke. Similarly, the recent findings from a prospective, population-based study ( $n = 9680$ ) from Rotterdam<sup>[7]</sup> showed low circulating vitamin D in prevalent stroke but only severe vitamin D deficiency was linked to incident stroke. The study concluded with a view that lower vitamin D levels might not lead to higher stroke risk, but rather could be an outcome of stroke.<sup>[7]</sup>

Given the inconsistent findings with a lack of reports on large sample sizes, the authors have indicated the limitations in inferring the causal association of vitamin D deficiency with stroke and have advocated that this should be explored in further studies.<sup>[3]</sup> Authors have also opined that a plausible causal relationship between vitamin D deficiency and risk of stroke cannot be excluded based on a recently published Mendelian randomized study.<sup>[3,8]</sup> In the referred study on

116,655 individuals, observational but not genetic low 25(OH)D concentration was linked to ischemic stroke; however, a causal relationship could be established between vitamin D deficiency and hypertension through the Mendelian randomization approach.<sup>[8]</sup> An interesting mechanistic and epidemiological intersection lies between vitamin D levels, risk of stroke, and hypertension, one of the most prevalent pathophysiological risk factors for stroke.<sup>[9]</sup> In a case-control study from China, the joint occurrence of vitamin D deficiency with hypertension was found to increase the probability of developing small vessel stroke by 5.6-fold [OR = 5.609 (95% CI 2.006–15.683)].<sup>[10]</sup> Similarly, in our cross-sectional evaluation in an Asian Indian population, the presence of hypertension was found to aggravate the risk of ischemic stroke associated with low vitamin D levels. We observed a distinct association between reduced circulating 25(OH)D and risk of ischemic stroke in hypertensives (OR = 13.54, 95% CI = 1.94–94.43) when compared to lack of association in non-hypertensives, ( $P_{interaction} = 0.04$ ).<sup>[11]</sup> The synergistic influence of severely deficient vitamin D status along with hypertension on an aggravated stroke risk needs meticulous assessment in a prospective and interventional manner to answer the issue of combined treatment of low vitamin D levels and/or hypertension to prevent stroke and reduce the severity of its outcomes.

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## REFERENCES

- Manousaki D, Richards JB. Commentary: Role of vitamin D in disease through the lens of Mendelian randomization-Evidence from Mendelian randomization challenges the benefits of vitamin D supplementation for disease prevention. *Int J Epidemiol* 2019;48:1435-7.
- Lutsey PL, Michos ED. Vitamin D, calcium, and atherosclerotic risk: Evidence from serum levels and supplementation studies. *Curr Atheroscler Rep* 2013;15:293.
- Kaul S, Manikanda J. Role of vitamin D in cerebrovascular disease. *Ann Indian Acad Neurol* 2021;24:142-5.
- Donkor ES. Stroke in the 21<sup>st</sup> century: A snapshot of the burden, epidemiology, and quality of life. *Stroke Res Treat* 2018;2018:3238165.
- Johnson W, Onuma O, Owolabi M, Sachdev S. Stroke: A global response is needed. *Bull World Health Organ* 2016;94:634.
- Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, *et al.* Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med* 2019;380:33-44.
- Berghout BP, Fani L, Heshmatollah A, Koudstaal PJ, Ikram MA, Zillikens MC, *et al.* Vitamin D status and risk of stroke: The rotterdam study. *Stroke* 2019 50:2293-8.
- Afzal S, Nordestgaard BG. Vitamin D, hypertension, and ischemic stroke in 116 655 individuals from the general population: A genetic study. *Hypertension* 2017. doi: 10.1161/HYPERTENSIONAHA.117.09411.
- Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, *et al.*

Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:227-76.

10. Si J, Li K, Shan P, Yuan J. The combined presence of hypertension and vitamin D deficiency increased the probability of the occurrence of small vessel disease in China. *BMC Neurol* 2019;19:164.
11. Majumdar V, Prabhakar P, Kulkarni GB, Christopher R. Vitamin D status, hypertension and ischemic stroke: A clinical perspective. *J Hum Hypertens* 2015;29:669-74.

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