

Role of Vitamin D in Cerebrovascular Disease

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Abstract

Introduction: Vitamin D deficiency is now a well-recognized public health problem affecting almost every second person throughout the world. Recent evidence from many population-based studies has indicated that a poor vitamin D status is a predictor of future strokes. **Materials and Methods:** We reviewed recent studies on 25-hydroxyvitamin D [25(OH)D] and symptomatic ischemic stroke. A graded increase in the risk of symptomatic ischemic stroke with decreasing levels of plasma 25(OH)D has been found in most of the studies. Vitamin D also has a role in the poststroke period where its deficiency may hinder the rehabilitation process. **Conclusions:** After reviewing current literature on the subject, we conclude that there are some data to suggest the role of vitamin D in patients with stroke but it cannot be concluded as a risk factor for stroke. Larger population-based studies are needed to confirm the causative role of vitamin D in stroke.

Keywords: Stroke, vitamin D, rehabilitation

INTRODUCTION

In the last few years, there have been several reports of a possible association between vitamin D deficiency and stroke. Being one of the leading preventable causes of death and disability worldwide,^[1,2] the reports of possible association between stroke and vitamin D deficiency assume importance.

Observational studies on vitamin D and stroke

In one of the earlier studies conducted in Auckland, healthy community-dwelling women (n = 1471) were followed over 5 years (1998–2003). There was an increased risk of stroke (hazard ratio [HR]: 1.7; 95% CI: 1.0, 3.0; *P* = 0.039) in women with seasonally adjusted 25-hydroxyvitamin D [25(OH)D] <50 nmol/L. After potential confounders (history of ischemic heart disease, stroke or TIA, dyslipidemia, and diabetes) were adjusted, the relation between a seasonally adjusted 25(OH)D concentration <50 nmol/L and increased risk of stroke were not statistically significant.^[3] According to Honolulu heart study including 7935 Japanese-American men, stroke risk was high in patients with low dietary vitamin D intake and was an independent predictor of strokes over 34 years of follow-up, during which 960 stroke events were recorded.^[4] The LUDwigshafen RiSk and Cardiovascular Health (LURIC) study included 3316 patients referred for coronary angiography between 1997 and 2000. 25(OH)D and 1,25-dihydroxyvitamin D [1,25(OH)2D] levels were measured in 3299 and 3315 study participants, respectively.^[5] After adjustment for several possible confounders, the odds ratios (with 95% CIs) for fatal strokes remained significant for 25(OH)D at 0.67 (0.46–0.97; *P* = 0.032) and for 1,25(OH)2D at 0.72 (0.52–0.99; *P* = 0.047). Low levels of 25(OH)D and 1,25(OH)2D were independently predictive of fatal strokes in this study.^[5] Several prospective observational studies have also shown vitamin D deficiency as a significant independent risk factor for stroke.^[6–9]

To explore the association between vitamin D status and the risk of stroke, a systematic review and meta-analysis were conducted including 19 studies. The pooled relative risk was 1.62 (95% CI: 1.34–1.96). On further analysis, vitamin D status was associated with ischemic stroke (relative risk = 2.45, 95% CI: 1.56–3.86), but not with hemorrhagic stroke (relative risk = 2.50, 95% CI: 0.87–7.15).^[8] Another meta-analysis by Wang *et al.* included 19 independent studies with 6123 CVD cases in 65,994 participants. On comparing lowest with the highest 25(OH)-vitamin D categories, the pooled relative risk was 1.52 (95% CI: 1.30–1.77) for total CVD and 1.64 (95% CI: 1.27–2.10) for stroke.^[10] This meta-analysis showed a linear, inverse association between circulating 25(OH)-vitamin D levels ranging from 20 to 60 nmol/L and risk of CVD and stroke.^[10] Brondum *et al.* measured plasma 25(OH)D levels in 10,170 individuals from the general population, in the Copenhagen City Heart Study.^[11] During 21 years of follow-up, 1256 and 164 persons developed ischemic and hemorrhagic stroke, respectively. Stepwise decreasing plasma 25(OH)D concentrations were associated with stepwise increasing risk of ischemic stroke.^[11] Comparing individuals with severe vitamin D deficiency (<25.0 nmol/L [*<*10.0 ng/mL]) to individuals with optimal vitamin D status (*≥*75.0 nmol/L

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Submitted: 25-Aug-2020 **Revised:** 09-Sep-2020 **Accepted:** 03-Nov-2020

Published: 25-Jan-2021

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DOI: 10.4103/aian.AIAN_928_20

[≥ 30.0 ng/mL]), the multivariate adjusted HR of ischemic stroke was 1.36 (1.09–1.70).^[11] In a meta-analysis including 10 studies, 58,384 participants and 2644 events, comparison of lowest versus highest quartile of 25(OH)D concentrations, the multivariate adjusted odds ratio of ischemic stroke was 1.54 (1.43–1.65).^[11] Results of these meta-analyses consistently indicate that low vitamin D status is a likely risk factor for stroke.

The causal association between serum vitamin D levels and the risk of ischemic stroke was studied recently in a Mendelian randomized study.^[7] It was shown in the study that serum vitamin D was one of the causal factors for ischemic stroke, and that the relationship between ischemic stroke and vitamin D could not be excluded. However, one recent study that combined the data of three population-based studies reported no significant association between vitamin D status and the incidence of hypertension and stroke.^[6,7] Overall, most of the observational studies have shown association between vitamin D and stroke risk but further studies with large sample sizes are needed to confirm or refute this association.

Interventional studies on vitamin D and stroke

Women's Health Initiative (WHI), the largest RCT in which 36,282 postmenopausal women were allocated to randomly receive daily either 400 international units (IU) of vitamin D with 1000 mg calcium or placebo over 7 years.^[12] The HR at the end of the study for fatal cerebrovascular events was 0.96 in the treatment versus the placebo group (95% CI: 0.82–1.10). Calcium and vitamin D supplementation neither increased nor decreased the risk for coronary heart disease or stroke in healthy postmenopausal women throughout the 7-year duration of this randomized trial. A low vitamin D dose of 400 IU/day and poor compliance were major limitations of the WHI trial.^[12]

Relation between vitamin D and stroke subtypes

In a South Indian study, a significant association between 25(OH)D deficiency and ischemic stroke subtypes was reported.^[13] Out of 250 patients with stroke, vitamin D deficiency was found in 50/91 patients (54.9%) with large vessel atherosclerosis, 20/45 patients (44.4%) with small vessel disease, 20/37 patients (54%) with cardioembolic stroke, 15/35 patients (42.8%) with stroke of other etiology, and 17/42 patients (40.4%) with stroke of undetermined cause.^[13] Multiple logistic regression analysis confirmed an independent association of 25(OH)D deficiency with ischemic stroke (odds ratio: 1.6; 95% CI: 1.2–2.8). This association was strongest with large artery atherosclerosis (odds ratio: 2.4; 95% CI: 1.6–3.5) and cardioembolic stroke (odds ratio: 2.0; 95% CI: 1.0–3.2).^[13]

Vitamin D and stroke outcome

One study of 386 stroke patients showed that 25(OH)D levels at hospital admission were associated with stroke severity, as well as with poor early functional outcomes.^[14] Considering that the association of low 25(OH)D with poor outcome at discharge remained significant even after adjustments for confounders including stroke severity, the authors hypothesized that

vitamin D might promote neuroplastic changes that may in turn improve clinical recovery.^[14] Since 25(OH)D can cross the brain–blood barrier and VDRs have been identified within the brain, it has been subsequently suggested that vitamin D may exert neuroprotective actions.^[15]

Musculoskeletal consequences of vitamin D deficiency in stroke

Musculoskeletal consequences of vitamin D deficiency are common in stroke patients and are the main rationale for evaluation, prevention, and treatment of vitamin D deficiency in patients with stroke. Based on the Institute of Medicine (IOM) systematic review^[16] and trials of vitamin D supplementation,^[17,18] maintaining a serum 25(OH)D levels between 20 and 40 ng/mL (50–100 nmol/L) is considered optimal. These recommendations are based on evidence in relation to bone health. According to a meta-analysis of seven randomized trials, cholecalciferol (vitamin D3) increased serum 25(OH)D concentrations more efficiently than ergocalciferol (vitamin D2).^[19]

Role of vitamin D in stroke rehabilitation

According to previous studies, 86–89% of patients in a rehabilitation care were found to have deficient levels of vitamin D,^[20] and other studies have also reported an association between functional recovery after stroke and serum vitamin D levels.^[21] Vitamin D is called a neurosteroid because of widespread distribution of vitamin D receptors on neuronal and glial cells and is considered to play a neuroprotective role.^[22,23] A recent review of meta-analysis has shown that a combination of vitamin D supplementation and exercise improved muscle strength and physical functioning.^[24] Therefore, supplementation of vitamin D may have additional benefits after acute stroke in terms of neurorehabilitation.

A recent randomized controlled trial conducted in Japan studied the effect of vitamin D supplementation on rehabilitation in stroke patients after the acute treatment.^[25] The vitamin D3 group had a higher mean Barthel Index efficiency than the placebo group (0.32 vs. 0.27), but the difference did not reach statistical significance ($P = 0.46$).^[25]

On the contrary, a recent randomized controlled trial showed that a single intramuscular injection of vitamin D (cholecalciferol 600,000 IU) had an improved Scandinavian stroke scale score at 12 weeks following acute stroke in vitamin D deficient patients.^[26] Another randomized trial showed an increased probability of survival at 24 weeks in acute stroke patients with vitamin D deficiency, after a single intramuscular injection of vitamin D (cholecalciferol 600,000 IU) followed by oral vitamin D (cholecalciferol 60,000 IU) once a month, and elemental calcium, 1 g/day.^[27]

Dosing

For patients with serum vitamin D levels < 12 ng/mL, rapid treatment with 50,000 IU orally once a week for 6–8 weeks followed by 800 IU daily is recommended. For subjects with serum vitamin D levels 12–20 ng/mL, supplementation with

800–1000 IU daily is recommended. For individuals with serum vitamin D levels of 20–30 ng/mL, daily supplementation with 600–800 units may be sufficient to maintain levels in the target range. Effectiveness of vitamin D treatment and compliance can be assessed by measuring 25(OH)D levels. Evaluation of vitamin D should not be done less than 3 months after starting vitamin D supplementation, as achieving a steady state in vitamin D levels takes some time.^[28]

Before prescribing vitamin D, it is important to enquire about additional dietary supplements patient may be taking, to prevent overdosing. Exogenous vitamin D toxicity (VDT) is usually caused by unsupervised prolonged intake of high doses of pharmacological preparations of vitamin D and is associated with hypercalcemia. Although VDT is rare, the health effects can be serious if it is not promptly identified. The initial effects of VDT are confusion, apathy, recurrent vomiting, abdominal pain, polyuria, polydipsia, and dehydration. These effects have been observed at vitamin D levels above 88 ng/mL.^[29] In 2010, safe upper limit of vitamin D was defined by IOM as 4000 IU/day.^[30]

It needs to be emphasized that a major part of our knowledge on beneficial effects of vitamin D is based on studies in which patients received concomitant vitamin D with calcium supplementation.^[31-33] The interactions of calcium and vitamin D combination therapies and their effects are not clear and further randomized studies are required to address these issues.

CONCLUSION

There is lack of robust data to consider Vitamin D deficiency as an independent risk factor for causing stroke. However, there are some data to suggest that vitamin D deficiency may contribute to musculoskeletal complaints in patients of stroke and also may hinder the rehabilitation process. So, while it may be premature to estimate Vitamin D levels as a risk factor for stroke, it is worthwhile to check vitamin D deficiency in all individuals of transient ischemic attack and stroke. The treatment needs proper doses under monitoring to prevent side effects.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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