25-Hydroxyvitamin D Status Is Associated With Chronic Cerebral Small Vessel Disease

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Background and Purpose—The aim of this study was to determine the association between 25-hydroxyvitamin D (25(OH)D) and neuroimaging correlates of cerebral small vessel disease.

Methods—We identified 759 consecutive patients with acute ischemic stroke or transient ischemic attack. Lacunes, white matter hyperintensity, and cerebral microbleed (CMB) were assessed using MR images. Deep CMB was defined as the presence of CMB in basal ganglia, thalamus, or brain stem. The association between 25(OH)D and small vessel disease was tested using linear and logistic regression analyses.

Results—Mean age was 68 (±13) years. Mean level of 25(OH)D was 34.1±17.8 nmol/L. On bivariate analysis, a 25-nmol/L decrease in 25(OH)D was associated with lacunes (regression coefficient, 0.23; 95% confidence interval [CI], 0.02–0.45), severe white matter hyperintensity (odds ratio, 2.05; 95% CI, 1.41–3.08), and deep CMB (odds ratio, 1.28; 95% CI, 1.01–1.63). Also, 25(OH)D deficiency (≤25 nmol/L) was associated with lacunes (regression coefficient, 0.5; 95% CI, 0.04–0.95), severe white matter hyperintensity (odds ratio, 2.74; 95% CI, 1.31–6.45), and deep CMB (odds ratio, 1.68; 95% CI, 1.03–2.78). The association remained significant even after multivariable adjustment and in the subgroup of previously healthy patients.

Conclusions—25(OH)D is inversely associated with lacunes, white matter hyperintensity, and deep CMB. Our findings suggest that 25(OH)D is linked to small vessel disease, and in future trials it should be tested whether 25(OH)D supplementation can prevent small vessel disease. **(*Stroke*. 2015;46:248-251. DOI: 10.1161/STROKEAHA.114.007706.)**

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During the past decade, increased attention has been paid to the nonskeletal targets of 25-hydroxyvitamin D (25(OH)D) such as brain, kidney, and blood vessels. Previous studies suggest that 25(OH)D is inversely associated with vascular risk factors, vascular diseases, and cognitive dysfunction.[1–7]

We hypothesized that cerebral small vessel disease (SVD) might be one of the links between vascular disease and cognitive dysfunction in patients with 25(OH)D deficiency. The aim of this study was to determine the association between 25(OH)D and neuroimaging correlates of SVD in patients with acute ischemic stroke or transient ischemic attack.

Methods

Study Population

Between May 2011 and December 2013, 838 consecutive patients with acute ischemic stroke or transient ischemic attack who visited a tertiary university hospital within 7 days of symptom onset were initially considered for inclusion in this study. The hospital is located in Seoul, South Korea and most of the patients were Koreans. Among these 838 patients, 79 patients (9%) were excluded from the analysis because the 25(OH)D level was not assayed in the blood sample. Therefore, 759 patients were ultimately enrolled and their data were analyzed. The baseline characteristics of the study population between before and after exclusion were not significantly different. This study was approved by the local institutional review boards.

25-Hydroxyvitamin D

The serum 25(OH)D level was measured using chemiluminescent immunoassay with ADVIA Centaur Vitamin D Total assay (Siemens Healthcare Diagnostics, Inc, NY). The 25(OH)D values <10 nmol/L were undetectable and were assigned 10 nmol/L. The intra- and interassay coefficients of variation were 5.1% and 4.4%, respectively. In addition to using 25(OH)D as a continuous variable, we treated 25(OH)D as a categorical variable and calculated the season-adjusted 25(OH)D level. The patients were categorized into the following 3 groups based on the 25(OH)D levels: sufficient (>50 nmol/L), insufficient (>25 and ≤50 nmol/L), or deficient (≤25 nmol/L). Season-adjusted 25(OH)D value was calculated by adding residuals from

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locally weighted polynomial regression of 25(OH)D on the month of blood draw to the overall mean value.

Brain MRI

Brain MRI was performed with a 3.0-T MR unit (Avanto, Philips, Eindhoven, The Netherlands). MRI was not available for the assessment of lacunes and white matter hyperintensity (WMH) in 36 patients (4.7%) and for the evaluation of cerebral microbleed (CMB) in 108 patients (14%). The assessment of neuroimages was done by 2 experienced neurologists (P.W.C. and K.Y.P.). MRI protocol; methods of assessing lacunes, WMH, and CMB; and inter-rater reliability are described in detail in the online-only Data Supplement.

Covariates

Our prospectively collected stroke database was reviewed retrospectively to assess the vascular risk factors and demographics of patients with acute ischemic stroke or transient ischemic attack. The definitions of vascular risk factors are described in the online-only Data Supplement.

Statistical Analyses

Bivariate analysis was performed using linear regression in which the dependent variable was 25(OH)D. Age, sex, hypertension, and variables whose *P* value was <0.15 on bivariate analysis were entered into the multivariate analyses. To investigate the association between 25(OH)D and SVD, bivariate and multivariate analyses were performed using linear regression for lacunes and logistic regression for WMH and deep CMB. The level of statistical significance was set at $P<0.05$. Statistical analysis was performed with R (Version 3.1.1, The R Foundation for Statistical Computing, Platform: 64-bit).

Results

The mean age of 759 patients was 68 (±13) years and mean level of 25(OH)D was 34.1 (±17.8) nmol/L. The levels of 25(OH)D were classified as sufficient in 122 patients (16%), insufficient in 358 patients (47%), and deficient in 279 patients (37%). Bivariate analysis showed that 25(OH)D was inversely associated with diabetes mellitus, WBC, total cholesterol, triglyceride, and HbA1c (Table 1).

Lacunes were found in 411 patients (57%; median 1; interquartile range, 0–2). WMH was assessed as grade 1 in 259 patients (36%), grade 2 in 173 patients (24%), and grade 3 in 90 patients (12%). CMB was present in 330 patients (51%) and deep CMB was found in 246 patients (38%). As the burden of lacunes, WMH, and deep CMB increases, the level of 25(OH)D decreases (Figure I in the online-only Data Supplement).

On bivariate analysis, a-25 nmol/L decrease in 25(OH)D was associated with lacunes (regression coefficient, 0.23; 95% confidence interval [CI], 0.02–0.45), severe WMH (odds ratio [OR], 2.05; 95% CI, 1.41–3.08), and deep CMB (OR, 1.28; 95% CI 1.01–1.63; Table 2). Also, 25(OH)D deficiency was associated with lacunes (regression coefficient, 0.5; 95% CI, 0.04–0.95), severe WMH (OR, 2.74; 95% CI, 1.31–6.45), and deep CMB (OR, 1.68; 95% CI, 1.03–2.78). The association remained significant even after adjustment for confounders.

25(OH)D and 25(OH)D deficiency were not associated with CMB in any location (OR [95% CI], 1.07 [0.86–1.34]; 1.11 [0.70–1.77], respectively).

When we used season-adjusted 25(OH)D as the outcome variable, the results were the same except that the association between 25(OH)D and deep CMB lacked statistical significance (Table I in the online-only Data Supplement).

Table 1. Baseline Characteristics of the Subjects

	All Patients (n=759)	25-Hydroxyvitamin D, nmol/L	
		RC (95% CI)	*P* Value
Demographics			
Age, y (mean±SD)	68.4±12.5	−0.03 (−0.13 to 0.07)	0.60
Females, n (%)	321 (42)	−2.47 (−5.03 to 0.09)	0.06
Hypertension, n (%)	431 (57)	−0.39 (−2.95 to 2.17)	0.77
Diabetes mellitus, n (%)	224 (30)	−3.64 (−6.41 to −0.87)	0.01
Ischemic heart disease, n (%)	63 (8)	1.78 (−2.81 to 6.37)	0.45
Atrial fibrillation, n (%)	203 (27)	1.60 (−1.26 to 4.46)	0.27
Current smoking, n (%)	199 (26)	−2.02 (−4.90 to 0.86)	0.17
Dyslipidemia, n (%)	44 (6)	0.72 (−4.71 to 6.14)	0.80
Previous stroke history, n (%)	137 (18)	−0.02 (−3.31 to 3.28)	0.99
Laboratory findings			
WBC, $\times 10^9$/L (mean±SD)	8.1±3.2	−0.43 (−0.83 to −0.04)	0.03
Total cholesterol, mmol/L (mean±SD)	4.6±1.2	−1.40 (−2.47 to −0.32)	0.01
LDL cholesterol, mmol/L (mean±SD)	2.7±0.9	−0.76 (−2.18 to 0.66)	0.29
Triglyceride, mmol/L (mean±SD)	1.4±1.0	−1.44 (−2.71 to −0.16)	0.03
HbA1c, % (mean±SD)	6.2±1.4	−1.47 (−2.40 to −0.55)	<0.01
Creatinine, μmol/L (mean±SD)	89.5±86.0	−0.01 (−0.03 to 0.004)	0.15
Calcium, mmol/L (mean±SD)	2.2±0.1	10.9 (−0.51 to 22.4)	0.06
Phosphorus, mmol/L (mean±SD)	1.1±0.4	2.48 (−0.58 to 5.53)	0.11

CI indicates confidence interval; HbA1c, glycohemoglobin; RC, regression coefficient; and WBC, white blood cell count.

Among the 759 patients, modified Rankin Scale score before stroke was zero in 529 patients (70%). Mean 25(OH)D level in these patients was 34.9 (±18.3) nmol/L. On multivariate analysis, a 25-nmol/L decrease in 25(OH)D was associated with lacunes (regression coefficient, 0.34; 95% CI, 0.10–0.58), severe WMH (OR, 2.14; 95% CI, 1.27–3.89), and deep CMB (OR, 1.36; 95% CI 1.01–1.84; Table II in the online-only Data Supplement).

Discussion

Our results showed that, on average, every 25 nmol/L decrease in 25(OH)D was associated with an increase in the number of lacunes by 0.23 and increased odds of severe WMH and deep CMB by 2.05 and 1.28, respectively. To the best of our knowledge, this is the first report demonstrating an association between 25(OH)D and various neuroimaging correlates of SVD.

Our results were consistent with those in a previous report by Buell et al,[5] which showed that 25(OH)D was inversely associated with WMH. In 318 elders (74±8 years) receiving home care, 25(OH)D insufficiency or deficiency was significantly associated with increased WMH. The presence of lacunes was also investigated and they were more prevalent in patients with 25(OH)D ≤50 nmol/L (20 ng/mL) than in patients with >50 nmol/L (24% versus 21%). However, these

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Table 2. Association Between 25(OH)D and Cerebral Small Vessel Disease

	Lacunes		WMH		Deep Microbleed	
	RC (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
A 25-nmol/L decrease in 25(OH)D						
Model 1	0.23 (0.02–0.45)	0.03	2.05 (1.41–3.08)	<0.01	1.28 (1.01–1.63)	0.04
Model 2	0.26 (0.05–0.47)	0.01	1.82 (1.24–2.77)	<0.01	1.29 (1.01–1.65)	0.04
Model 3	0.26 (0.05–0.48)	0.02	1.79 (1.21–2.73)	<0.01	1.34 (1.05–1.72)	0.02
25(OH)D, 3 groups						
Model 1						
Sufficient	Reference	…	Reference	…	Reference	…
Insufficient	0.47 (0.03–0.91)	0.04	1.59 (0.75–3.77)	0.26	1.34 (0.84–2.19)	0.23
Deficient	0.50 (0.04–0.95)	0.03	2.74 (1.31–6.45)	0.01	1.68 (1.03–2.78)	0.04
Model 2						
Sufficient	Reference	…	Reference	…	Reference	…
Insufficient	0.47 (0.05–0.89)	0.03	1.78 (0.82–4.35)	0.17	1.42 (0.87–2.35)	0.16
Deficient	0.54 (0.10–0.98)	0.02	2.60 (1.20–6.29)	0.02	1.73 (1.05–2.91)	0.04
Model 3						
Sufficient	Reference	…	Reference	…	Reference	…
Insufficient	0.46 (0.03–0.89)	0.04	1.71 (0.77–4.19)	0.21	1.50 (0.91–2.52)	0.11
Deficient	0.54 (0.09–0.99)	0.02	2.47 (1.13–6.05)	0.03	1.84 (1.10–3.14)	0.02

Model 1 is the bivariate analysis. Model 2 is adjusted for age, sex, hypertension, diabetes mellitus, white blood cell, total cholesterol, triglyceride, and glycohemoglobin. Model 3 is adjusted for calcium, phosphorus, and the variables entered in model 2. 25(OH)D indicates 25-hydroxyvitamin D; CI, confidence interval; OR, odds ratio; RC, regression coefficient; and WMH, white matter hyperintensity.

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results did not reach statistical significance probably because of lack of power. In our study, both lacunes and WMH showed a significant inverse association with 25(OH)D.

Michos et al[8] investigated the association between 25(OH)D and WMH in 833 whites and 789 blacks and found no significant association. Although the size of study population of their study was large, demographics suggested that their study population should be at a lower risk of vascular disease than our study population. For example, the mean age was 62 years, 47% of patients had hypertension, 17% of patients had diabetes mellitus, and mean 25(OH)D level was 55 nmol/L. In our study, mean age was 68 years, 57% of patients had hypertension, 30% of patients had diabetes mellitus, and mean 25(OH)D level was 34 nmol/L. A larger sample size might be needed to demonstrate a moderate association between 25(OH)D and WMH in a population-based study in patients with low vascular risk.

25(OH)D was reported to be associated with arterial stiffness, which could result in increased pulse pressure.[9–11] Because the brain has a low vascular resistance, exposure to highly pulsatile systemic pressure could damage the small arteries of the brain.[11]

Our results also showed that 25(OH)D was inversely associated with deep CMB, but not with CMB in any location. Because deep CMB was reported to be associated with hypertensive brain injury,[12,13] 25(OH)D might be inversely associated with increased hypertensive insult.

In addition, 25(OH)D was reported to promote endothelium-dependent vasodilation.[14] Through these presumed mechanisms, 25(OH)D might contribute to the brain damage associated with SVD.

The present study has the following limitations. First, because this study is a cross-sectional analysis, we cannot assume a causal relationship between 25(OH)D and SVD. In particular, there is a possibility of reverse causal relation. Low 25(OH)D level might be a consequence of decreased physical activity because of the burden of SVD. We performed the additional analysis, which included only previously healthy patients. In this subgroup analysis, the result was the same with that in the whole cohort. Therefore, the possibility of reverse causal relationship might be low in our study. Second, the data on vitamin D supplementation, nutrition, health education, social level, and parathyroid hormone level were not available. Therefore, we could not adjust multivariable analysis for these variables, although their role in the association between 25(OH)D and SVD has not been clarified yet. Third, this study was based on the single center located in Seoul, South Korea. Also, our study population had high prevalence of 25(OH)D insufficiency or deficiency (84%) and low rate of hypertension and diabetes mellitus (57% and 30%, respectively). Whether our finding can be reproduced in another ethnicity or area should be tested in the future study.

In conclusion, 25(OH)D is inversely correlated with lacunes, WMH, and deep CMB. Our results suggest that 25(OH)D is linked to chronic brain injury associated with SVD, and in future trials it should be assessed whether 25(OH)D replacement can prevent or reduce the burden of SVD.

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Disclosures

None.

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