

Association between Serum 25-Hydroxyvitamin D Level and Cognitive Impairment in Patients with White Matter Lesions: A Cross-Sectional Study

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Highlights of the Study

- Vitamin D deficiency was associated with multiple areas of cognitive impairment.
- It is an independent risk factor for cognitive impairment in patients with white matter lesions.

Keywords

25-hydroxyvitamin D · Cognitive impairment · White matter lesions · Montreal Cognitive Assessment

Abstract

Objectives: We aimed to observe the relationship between serum 25-hydroxyvitamin D (25-[OH] D) and different cognitive domains, and to evaluate the predictive value of 25-(OH) D level for cognitive impairment in patients with white matter lesions (WML). **Methods:** The differences in clinical data including 25-(OH) D were analyzed between cognitive normality ($n = 87$) and impairment ($n = 139$) groups, and variant cognitive domains were analyzed between groups of different levels of serum 25-(OH) D. Risk factors for cognitive impairments were evaluated with multivariate logistic regression analysis; a receiver operating characteristic (ROC) curve of 25-(OH) D levels was used to examine the association be-

tween 25-(OH) D and WML with cognitive dysfunction. **Results:** As the severity of WML increased, the proportion of patients with a low level of serum 25-(OH) D increased ($p < 0.05$). The total MoCA (Montreal Cognitive Assessment) scores and all domain scores except naming were significantly lower in patients with low levels of serum 25-(OH) D than in patients with high levels of serum 25-(OH) D ($p < 0.05$). Multivariate logistic regression analyses showed that serum 25-(OH) D levels were independently correlated with cognitive impairment. In the ROC analysis, the optimal cut-off value for 25-(OH) D was 17.53 with 76% sensitivity and 70% specificity (AUC = 0.751, 95% CI: 0.674–0.819, $p < 0.05$). **Conclusion:** We observed that vitamin D deficiency is associated with multiple areas of cognitive impairment and that it is an independent risk factor for cognitive impairment in WML.

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Introduction

White matter lesions (WML), the presence of white matter hyperintensity on T₂ fluid-attenuated inversion recovery (FLAIR) magnetic resonance images (MRI), have a prevalence rate of 60–80% in adults over 65 years of age [1]. The pathogenesis of WML has been attributed to chronic ischemia caused by cerebral small vessel disease (CSVD) [2] and white matter demyelination, or both [3]. Recently, WML has also been shown to be associated with microembolization originating from the carotid plaque, subcortical vascular dementia (SVaD), ischemic stroke, etc. [4, 5]. SVaD has been employed to define a circumscribed syndrome, related to small vessel disease [6]. The brain imaging would show either the Binswanger-type WML or lacunar infarcts with the absence of cortical nonlacunar territorial infarct and other causes of WML. Moreover, there is substantial evidence in SVaD of an associated hypoperfusive course due to the altered caliber of small arteries, and this is associated with incomplete ischemia of the deep white matter [7]. However, from a neuropsychological perspective, CSVD has been traditionally distinguished from SVaD [3]. Studies have shown that deep white matter hyperintensities seen on MRI do not correlate with impairments, and they should be considered as “epiphenomena that morphologically characterize CSVD, but do not indicate cognitive impairment [8].” In addition, controversial aspects of the pattern progression from small vascular disease to subcortical dementia include time course, contributing factors, and individual variability [6]. Clinically, the risk factors for WML include hypertension, dyslipidemia, diabetes mellitus, and smoking [9]. WML, especially periventricular WML, is often accompanied by cognitive decline and an increased risk of dementia in the general population [10]. Therefore, early diagnosis and prediction of risk factors for the occurrence and progression of WML are of great significance.

Epidemiological studies have shown that vitamin D deficiency is common in the middle-aged and elderly population [11], which might be due to the decreased ability of the skin to synthesize vitamin D precursors and decreased ability to conduct outdoor activities, leading to insufficient exposure to sunshine in this population. It was traditionally thought that vitamin D mainly regulates calcium and phosphorus metabolism in the body. Recent studies have shown that vitamin D is also involved in the occurrence of aging disorders of cardiovascular and cerebrovascular events [12], including CSVD [13]. Low levels of serum vitamin D are associated with higher prevalence

of cognitive decline even in a longitudinal study of non-elderly adults [14]. On the other hand, the serum level of 25-hydroxyvitamin D (25-[OH] D), a well-known marker of vitamin D status [15], is inversely associated with WML [13]. But the relationship between serum vitamin D and cognitive function in patients with WML remains unclear. The objective of this study was to study the relationship between serum level of 25-(OH) D and cognitive scores in patients with WML.

Materials and Methods

Study Population and Data Collection

Consecutive patients from a single academic center, the Department of Neurology of the General Hospital of Wanbei Coal and Electrical Group were prospectively enrolled in this study from July 2017 to March 2018. Inclusion criteria were: (1) age 40–75 years; (2) deep white matter or paraventricular abnormal signals on 1.5-T head MRI scan showing hypointensity on T1-weighted imaging and hyperintensity on FLAIR and T2-weighted imaging. The following patients were excluded: (1) patients with nonangiogenic WML and diseases that may affect cognitive impairment, such as infection, poisoning, immune demyelination, etc.; (2) patients with acute and chronic inflammation, rheumatic immune disease, dementia, malignant tumor, blood system disease, severe liver and kidney dysfunction; (3) patients who were given vitamin D or other drugs affecting bone metabolism in the last 3 months; (4) patients with mental or other diseases which may affect their cooperation in the test.

Clinical information including demographic data, education level, past medical and stroke history, current cigarette smoking, and alcohol consumption were collected from all patients.

Acquisition and Analysis of Images

Imaging of the brain was performed with a 1.5-T MRI scanner (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany) using a standard MRI protocol including T1 sagittal/axial, T2 axial, FLAIR axial, and diffusion-weighted sequences.

WML was evaluated in 3 grades from the T2-weighted FLAIR MR images, under the supervision of two neuroradiologists (X.-M.Z. and X.-Z.Y.), using the modified Fazekas's visual scale [16], which has been widely applied as a scale to grade WML severity in epidemiological studies [17]; briefly: grade 1, mild lesions: cap-like or pencil-thin lining; grade 2, moderate lesions: a smooth halo; grade 3, severe lesions: large confluent areas.

Assessment of Serum 25-(OH) D

Venous blood was collected from participants at the time of brain imaging acquisition. Serum 25-(OH) D concentration, an effective indicator of vitamin D status [18], was measured by chemiluminescence immunoassay (Cobase 6000, Roche Diagnostics, Switzerland). It has been reported that a 25-(OH) D concentration of more than 20 ng/mL can meet human health needs [19]. Therefore, WML patients were divided into two groups with 25-(OH) D <20 ng/mL and 25-(OH) D ≥20 ng/mL.

Table 1. Demographic characteristics of the patients with or without cognitive impairment

Characteristics	Cognitive impairment group (n = 139)	Normal cognition group (n = 87)	t/Z/ χ^2 value	p
Male gender, n (%)	78 (56.1)	45 (51.7)	0.416	0.519
Age, years	65.0 [61.00, 71.00]	59.00 [51.00, 64.00]	5.508	0.000*
Lower education, n (%)	65 (46.8)	15 (17.2)	20.392	0.000*
Smoking, n (%)	45 (32.4)	18 (20.7)	3.634	0.057
Alcohol, n (%)	34 (24.5)	18 (20.7)	0.429	0.512
Stroke, n (%)	37 (26.6)	13 (14.9)	4.234	0.040*
Hypertension, n (%)	96 (69.1)	34 (39.1)	19.689	0.000*
Diabetes, n (%)	33 (23.7)	11 (11.5)	5.209	0.040*
Hyperlipemia, n (%)	66 (47.5)	40 (46.0)	0.001	0.979
Coronary disease, n (%)	30 (20.1)	10 (11.5)	3.739	0.053
TG, mmol/L	1.3 [1.00, 1.97]	1.29 [0.91, 1.95]	0.627	0.530
TC, mmol/L	4.7±1.04	4.52±0.98	1.797	0.074
LDL, mmol/L	2.5 [2.01, 3.04]	2.62 [2.20, 3.15]	-1.066	0.286
HDL, mmol/L	1.1 [2.01, 3.04]	1.18 [1.06, 1.37]	-1.909	0.056
Glucose, mmol/L	5.4 [4.97, 6.30]	5.38 [4.95, 5.86]	0.632	0.527
Systolic pressure, mm Hg	150.0 [136.0, 164.0]	137.0 [121.00, 152.00]	4.554	0.000*
Diastolic pressure, mm Hg	83.0 [76.0, 90.0]	83.0 [73.00, 93.00]	0.379	0.705
Hcy, μ mol/L	13.0 [10.0, 17.0]	11.0 [9.00, 16.00]	2.366	0.018*
Uric acid, mmol/L	388.0 [340.0, 434.0]	334.0 [295.00, 398.00]	4.015	0.000*
25-(OH) D, ng/mL	15.44±5.71	21.44±7.17	-6.608	0.000*

Values are presented as n (%), mean \pm standard deviation, or median [25th and 75th interquartile range]. LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; Hcy, homocysteine. * $p < 0.05$, for the pairwise comparison between the cognitive impairment group and normal cognition group.

The levels of LDL, HDL, glucose, homocysteine (Hcy), and uric acid were measured by an Automatic Biochemical Analyzer (HITACHI7600-020, Japan).

Neuropsychological Assessment

Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) [20] were used to evaluate the cognitive function of the patients. The MMSE scale, with a total score of 30 points, consisted of orientation, memory, attention and calculation, language function, and memory. Cognitive impairment was determined with MMSE score < 17 in patients with educational level of illiteracy, < 20 in patients with elementary school education, and < 26 in patients with junior high school or higher education; otherwise, normal cognitive function was determined. Due to the high sensitivity and specificity of the MoCA scale in recognizing impairment in various domains of cognitive function [21], MoCA was employed to evaluate the 7 cognitive domains: visual space and executive function, naming, attention and calculation, language, abstraction, delayed recall, and orientation. All scales were evaluated by trained physicians in the Department of Neurology.

Statistical Analysis

SPSS statistical software (version 23.0, Chicago, IL, USA) was used to process the data, and normal distribution and homogeneity of variance tests were performed for each group. Continuous vari-

ables with normal distribution were presented as mean values \pm standard deviation. One-way analysis of variance (ANOVA) was used to analyze the differences among groups. Continuous variables with non-normal distribution were presented as median (four percentile) (25th and 75th interquartile range), and the Kruskal-Wallis test was used to analyze the differences among groups. Categorical variables were expressed as percentages, and the χ^2 test was used to analyze the differences between groups. Multivariate logistic regression analyses were conducted to estimate the odds ratios, with cognitive function used as dependent variable and age, gender, hypertension, diabetes, stroke, lipid, Hcy, uric acid, 25-(OH) D, current smoking and alcohol consumption, lower education used as independent variables. p values < 0.05 were considered statistically significant. The receiver operating characteristic (ROC) curve was used to show the sensitivity and specificity of 25-(OH) D and the optimal cut-off value for predicting patients with cognitive impairment.

Results

A total of 226 eligible participants with WML (54.42% male; mean age 62.61 ± 9.11 years) were enrolled in this study. Based on the presence or absence of cognitive

Table 2. Relationship between 25-(OH) D and the severity of WML

WML	<i>n</i>	25-(OH) D <20 ng/mL	25-(OH) D ≥20 ng/mL	χ^2 value	<i>p</i>
Mild	123	60 (48.8)	63 (51.2)	6.248	0.044
Moderate	51	29 (56.9)	22 (43.1)		
Severe	52	36 (69.2)	16 (30.8)		

Trend test: $\chi^2 = 6.150, p = 0.013$.

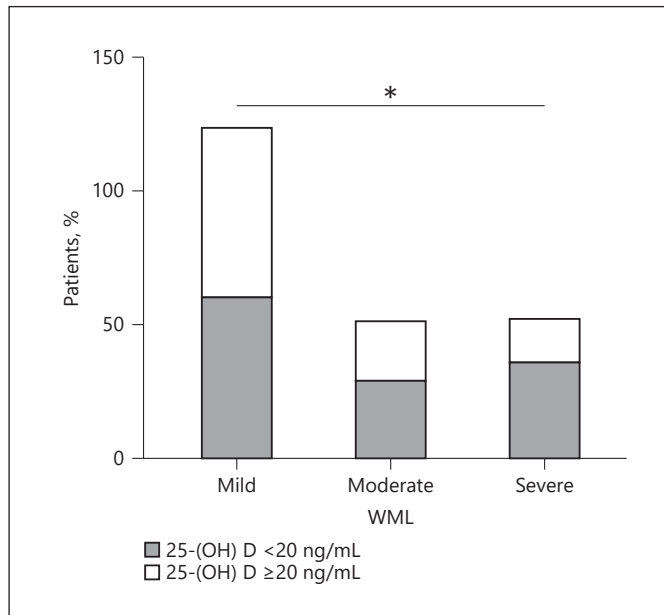


Fig. 1. Relationship between 25-(OH) D and WML severity. Comparison between the three groups, $\chi^2 = 6.248, * p < 0.05$; the level of 25-(OH) D decreased gradually with the aggravation of the lesion, trend test: $\chi^2 = 6.248, p = 0.013$.

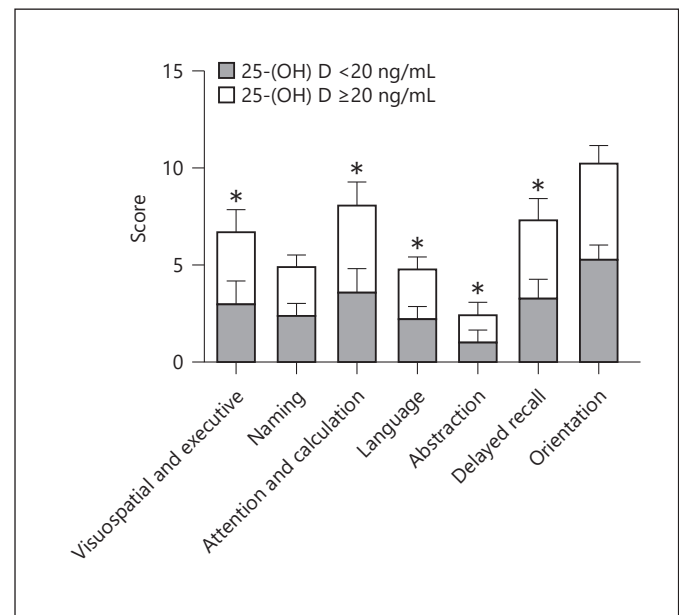


Fig. 2. Relationship between 25-(OH) D and cognitive domains in patients with WML. Comparison between the two groups, $* p < 0.05$.

impairment, the baseline clinical and laboratory characteristics of the subjects are depicted in Table 1. Out of the 226 patients with WML, 139 (61.50%) were found to have cognitive impairment. Patients with cognitive impairment were older than those with normal cognitive function ($p = 0.000$; Table 1). The proportion of patients with fewer years of education, hypertension, diabetes, stroke history, and systolic blood pressure, was significantly higher in patients with cognitive impairment compared to patients with normal cognitive function. And the patients with cognitive impairment had higher levels of serum Hcy and uric acid and significantly decreased levels of serum 25-(OH) D than those with normal cognitive function ($p < 0.05, p < 0.01$; Table 1). There were no significant differences in sex

ratio, in proportion of patients with smoking, drinking, coronary heart disease, hyperlipidemia, in levels of plasma total cholesterol (TC), triglycerides, LDL, HDL, blood glucose, and in diastolic blood pressure between the groups (Table 1).

The relationship between the severity of WML and vitamin D levels is given in Table 2. As the severity of WML increased, the proportion of patients with a low level of serum 25-(OH) D increased, while the proportion of patients with a high level of serum 25-(OH) D decreased. There was a statistical difference between groups ($p = 0.044$; Table 2 and Fig. 1).

The relationship between 25-(OH) D and different cognitive domains in patients with WML is shown in Table 3. The total scores of MoCA and domain scores of

Table 3. Relationship between 25-(OH)D and different cognitive domains in patients with WML

MoCA	25-(OH) D <20 ng/mL (n = 125)	25-(OH) D ≥20 ng/mL (n = 101)	t	p
Total score	20.57±4.48	23.64±4.94	4.902	0.000
Visuospatial	2.94±1.22	3.71±1.21	4.783	0.000
Naming	2.37±0.65	2.50±0.61	1.495	0.136
Attention and calculation	3.56±1.25	4.48±1.23	5.504	0.000
Language	2.18±0.68	2.58±0.62	4.644	0.000
Abstraction	1.00±0.62	1.42±0.65	4.889	0.000
Delayed recall	3.28±0.98	4.00±1.13	5.123	0.000
Orientation	5.23±0.77	5.00±0.92	2.063	0.053

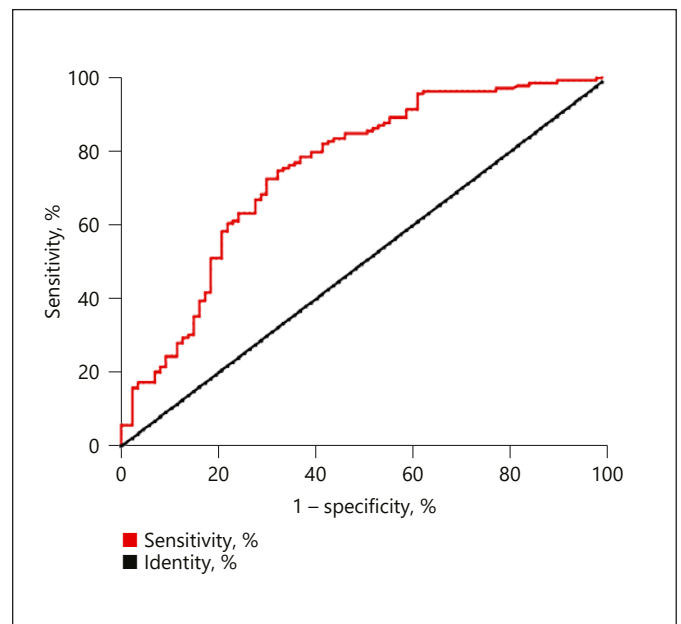
Table 4. The independent risk factors for cognitive impairment in patients with WML

	B	SE	Wald χ^2 value	p	OR (95% CI)
Age	0.064	0.031	4.277	0.039	1.066 (1.003, 1.133)
Lower education level	1.031	0.480	4.605	0.032	2.803 (1.093, 7.183)
Hypertension	1.082	0.510	4.495	0.034	2.950 (1.085, 8.020)
Systolic pressure	0.037	0.017	5.036	0.025	1.038 (1.005, 1.072)
Stroke	2.009	0.575	12.198	0.000	7.455 (2.415, 23.016)
TC	1.441	0.655	4.836	0.028	0.237 (0.065, 0.855)
Uric acid	0.008	0.003	5.315	0.021	1.008 (1.001, 1.015)
25-(OH) D	-0.235	0.046	25.643	0.000	0.790 (0.722, 0.866)

visuospatial and executive functions, attention and calculation, language, abstraction, and delayed recall in patients with low levels of 25-(OH) D were lower than in patients with high levels of 25-(OH) D ($p < 0.05$), whereas there was no significant difference in naming and orientation between the two groups ($p > 0.05$; Table 3 and Fig. 2).

We further performed multivariate logistic regression analyses to determine whether the 25-(OH) D levels were independently associated with cognitive impairment in patients with WML after adjustment for other confounding factors shown in Table 1. As shown in Table 4, age, fewer years of education, history of hypertension, history of stroke, systolic blood pressure, and levels of TC, uric acid, and 25-(OH) D remained independently correlated with cognitive impairment in patients with WML.

The ROC curve analysis performed to assess the predictive value of 25-(OH) D for cognitive impairment and using the optimal 25-(OH) D cut-off value of 17.53 ng/mL for cognitive impairment gave a sensitivity of 76% and a specificity of 70% (AUC = 0.751, 95% CI: 0.674–0.819; Fig. 3).

**Fig. 3.** ROC analysis of 25-(OH) D levels for cognitive impairment in patients with WML.

Discussion

The main findings of this study are that with the aggravation of WML, the incidence of cognitive impairment is significantly increased, and the low level of serum 25-(OH) D was closely related to the cognitive domains of visuospatial and executive functions, language, attention and calculation, delayed recall, and abstraction in patients with WML. A low level of 25-(OH) D was an independent risk factor for cognitive impairment in patients with WML. Age, fewer years of education, history of hypertension, history of stroke, systolic blood pressure, TC, and uric acid were risk factors for cognitive dysfunction in patients with WML. These risk factors were concordant with literature reports on the correlation with WML [9].

The mechanisms by which vitamin D affects cognitive function in WML remain unclear. Several studies have shown that WML is a type of CSVD [22], and its pathological lesion has been attributed to hypoperfusion, defective cerebrovascular reactivity, and dysfunction of the blood brain barrier. Vitamin D deficiency increases the risk of neurological deterioration [23] and is associated with reduction of subcortical volume and disruption of structural connectivity in patients with cognitive impairment. Consistent with this structural alteration associated with vitamin D deficiency, we found that the proportion of patients with low level of serum 25-(OH) D, a well-known marker of vitamin D status [15], increased as the severity of WML increased. On the other hand, structural changes have been shown to be correlated with cognitive impairment in patients with WML [24], and a large cohort study showed that WML contributes to the atrophy of brain regions related to AD dementia, and preventive therapy reducing the development of WML could decrease the incidence, or delay the onset, of dementia [25]. Vitamin D may also exert its functions directly through its receptors expressed on neurons affecting cognitive function, as it has many other functions, such as antioxidant and antiapoptotic effects on neurons, promoting the effect of neural conduction in the central nervous system [26], and decreasing the effect of amyloid plaques [27].

Our study had some limitations. Firstly, we only grouped the degree of WML lesions according to the Fazakas scale and did not further analyze the relationship between the levels of 25-(OH) D and the different locations of WML in patients with cognitive impairment. Studies have reported that periventricular WML are more likely to lead to cognitive impairment than deep WML,

especially the decline in information processing ability [28]. Another important limitation of this study is that 25-(OH) D levels are affected by many confounding factors, such as season, diet, sunshine time, etc., which are difficult to control [29]. Thirdly, MoCA is the only way to evaluate cognitive impairment, which can be comprehensively evaluated through questionnaires in a future study. Meanwhile, the study lacks a follow-up and a definition of the passage between WML and sVAD or small vessel disease-related dementia.

Conclusion

We confirmed that vitamin D deficiency is associated with multiple areas of cognitive impairment and that it is an independent risk factor for cognitive impairment in WML. This is a cross-sectional pilot study with a limited number of subjects and can only establish association. Therefore, a large-scale study is required to ascertain the association between vitamin D deficiency and cognitive impairment in WML.

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Statement of Ethics

Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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