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A cohort study of relationship between serum calcium levels and cerebral microbleeds (CMBs) in ischemic stroke patients with AF and/or RHD

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Abstract

Calcium is an essential element for life and has cerebroprotective property in stroke patients. Low serum calcium levels were found to be related to large hematoma volumes in intracerebral hemorrhagic patients and hemorrhagic transformation in ischemic stroke patients after thrombolysis. However, their impact on hemorrhage-prone small vessel disease represented by cerebral microbleeds (CMBs) is uncertain. We aim to investigate whether low serum calcium levels are associated with presence and location of CMBs.

Ischemic stroke patients with atrial fibrillation (AF) and/or rheumatic heart disease admitted to our hospital were consecutively and prospectively enrolled. Demographic and clinical information were collected and analyzed according to the occurrence and location of CMBs, and levels of serum calcium. We used logistic regression analysis to estimate the multivariable adjusted relationship between serum calcium levels and the presence or location of CMBs.

Among the 67 patients (28 males; mean age, 67.3 years) in the final analysis, 39 (58.2%) were found to have CMBs. After adjustment for age, sex, smoking habits, drinking habits, and renal impairment, the presence of CMBs and deep CMBs was, respectively, 4.96- and 4.83-fold higher in patients with lower serum calcium levels ($\leq$2.15 mmol/L) than in patients with higher serum calcium levels.

Lower serum calcium levels ($\leq$2.15 mmol/L) are independently associated with the presence of CMBs and deep CMBs in ischemic stroke patients with AF and/or rheumatic heart disease, which should be verified and extended in large cohorts, with other types of stroke patients and the general population.

Abbreviations: AF = Atrial fibrillation, CMBs = Cerebral microbleeds, HDL = high-density lipoprotein, ICH = Intracerebral hemorrhage, IS = Ischemic stroke, LDL = low-density lipoprotein, NIHSS = National Institutes of Health Stroke scale, RHD = Rheumatic heart disease, SWI = Susceptibility-weighted imaging, TG = triglycerides.

Keywords: atrial fibrillation, cerebral microbleeds, ischemic stroke, rheumatic heart disease, serum calcium levels

1. Introduction

Cerebral microbleeds (CMBs) are detected as small, rounded hypointense lesions on T2* or susceptibility-weighted imaging (SWI), and are focal hemosiderin deposit resulting from minimal blood leakage from damaged small vessels, which are regarded as markers of pathological vascular changes.[1,2] CMBs are frequently observed in patients with intracerebral hemorrhage (ICH),[3] ischemic stroke (IS),[3,4] vascular cognitive impairment,[5] and even in healthy elderly individuals.[6] Considering those, CMBs can predict risk of subsequent stroke, including ICH and IS,[3–4] and are also a predictor of cognitive impairment and neurodegeneration,[6–8] which has evoked great attention for its adverse effect on individuals.

The pathophysiologic features of CMBs can differ according to their location, with lobar (strictly in the lobar region) CMBs attributable to cerebral amyloid angiopathy, whereas deep (basal ganglia, thalamus, and brainstem) CMBs are indicative of hypertensive vasculopathy.[1,9,10] Despite those, the molecular mechanisms involved in CMBs are still argued and remain to be clarified.

Calcium is an essential element for life and has cerebroprotective property in stroke through neurovascular mechanism. According to the previous studies, low serum calcium levels attribute to poor outcome, extensive infarction in patients with IS, and large hematoma volumes in patients with ICH.[11–14] Recently, a study[15] in China indicated that low serum calcium

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was independently associated with hemorrhagic transformation in acute IS patients after thrombolysis. However, little attention has been paid to its roles in hemorrhage-prone small vessel disease represented by CMBs. The Kashima Scan Study,[16] a population-based cohort study, demonstrated that hypertension and lower calcium intake had joint effects on the risk of CMBs in healthy individuals.

Considering all these aforementioned studies about calcium, we studied their relation to CMBs in IS patients with atrial fibrillation (AF) and/or rheumatic heart disease (RHD), testing the hypothesis that low level of serum calcium is correlated with presence and the location of CMBs.

2. Methods

This research project was carried out under the auspices of the National Natural Science Foundation of China "Study on small vessel pathological mechanism of cerebral hemorrhage after cardioembolic stroke using SWI markers." The study protocol was approved by the biomedical ethics committee of West China Hospital. Written informed consent was obtained from participants or their guardians.

IS patients with AF and/or RHD were prospectively and consecutively enrolled after admission to West China Hospital, Sichuan University, Chengdu, China, between January 2014 and September 2015. To be enrolled, patients had to be with a diagnosis of stroke according to World Health Organization criteria,[17] further confirmed by computed tomography scanning or magnetic resonance imaging. AF was defined as a history of persistent AF or paroxysmal AF, supported by past ECG or diagnosed by the attending physicians based on ECG and/or 24-h ECG monitoring during admission.[18] RHD was diagnosed according to International Classification of Diseases, 10th ed., criteria and further confirmed by echocardiography.[18] Patients were excluded from the study if they were reluctant to participate in the registration; if they did not undergo SWI or serum calcium analysis or if serum calcium levels were not obtained within 48 h after admission.

A standardized form was used to collect data on patient baseline information, including demographic characteristics, stroke severity on admission, risk factors (including hypertension, diabetes mellitus, hyperlipidemia, previous transient ischemic attacks, history of stroke, and current smoking and alcohol consumption), renal impairment (medical history or eGFR <60 mL/min/1.73 m).[18] Stroke severity[19] on admission was measured using the National Institutes of Health Stroke scale.

Venous blood samples (4–6 mL) were collected from all patients within 48 h after admission. Serum levels of calcium were measured using Roche modular DDP analyzer (Roche, Switzerland). The normal reference values of serum calcium range from 2.1 to 2.7 mmol/L.

All participants were scanned at the Huaxi MR Research Center using a dedicated 3-T MRI system (Siemens Trio). The imaging protocol included the following pulse sequences: T1-weighted, fluid-attenuated inversion recovery sequence, T2-weighted, and axial SWI. Fluid-attenuated inversion recovery (repetition time = 6000 ms; echo time = 100 ms; echo time s = 93ms; flip angle = 90°; slice thickness = 5 mm; 21 slices; interslice gap = 1.5; field of view = 220 × 200 mm; matrix = 256 × 256), and SWI images (multislice gradient echo sequence; repetition time = 207ms; echo time = 20 ms; flip angle = 15°; slice thickness = 2 mm; 60 slices; no interslice gap; whole brain coverage; field of view = 220 × 173 mm; matrix = 256 × 256) were obtained from all subjects.

CMBs were defined as homogeneous, round focal areas observed throughout the brain, with a diameter less than 10 mm and very low signal intensity on SWI,[20]and were classified as lobar, cortical, corticosubcortical, deep, or infratentorial.[1,8] The location of the CMBs was classified as: strictly lobar CMBs and deep or infratentorial CMBs (with or without concomitant lobar CMBs).[21,22]

The presence and location of CMBs on SWI was determined independently by 2 neurologists blinded to clinical data. In case of disagreement, a third neurologist was consulted, and a consensus decision was reached. Our interrater reliability for accessing quality items was good ($k = 0.73$).

The $\chi 2$ or Fisher exact tests were used to compare categorical variables. Analysis of variance or Mann–Whitney U tests were used to compare continuous variables when appropriate. Binary logistic regression model was used to evaluate the association between variables and CMBs occurrence or location. When appropriate, results were reported as an odds ratio (OR) and 95% confidence interval (CI). Two-sided values of $P < 0.05$ were considered statistically significant. All statistical analyses were performed using SPSS version 20.0 (IBM, Chicago, IL).

3. Results

A total of 140 consecutive IS patients with AF and/ or RHD were enrolled in the study, but 48 (34.3%) were excluded because they did not complete SWI and another 25 (17.9%) were excluded because serum calcium levels within 48 h after admission were unavailable. Of 67 patients included in the final analysis, 28 (41.8%) were men, and mean age at stroke onset was 67.3 ± 11.98 years.

CMBs were detected in 39 patients (58.2%). Of these, 14 had single CMBs, and 25 had multiple CMBs (≥2). CMBs were most commonly present as deep or infratentorial bleeding (26/39, 67%), followed by strictly lobar bleeding (13/39, 33%). Baseline characteristics of IS patients with AF and/or RHD are shown in Table 1 according to whether they had CMBs. Patients with CMBs were more likely to be older and have history of hypertension (all $P < 0.05$, Table 1).

In the study, the serum calcium levels ranged from 1.89 to 2.57 mmol/L (mean value, 2.22 mmol/L). The distributions of serum calcium levels according to CMBs presence and location are shown in Fig. 1. Patients were subgrouped into tertiles based on serum levels of calcium within 48 h after admission (Table 2): tertile 1, <2.15 mmol/L; tertile2, 2.15–2.26 mmol/L; and tertile3, >2.26 mmol/L.

As shown by Table 2, patients in the lowest tertile of serum calcium were more likely to be older and have renal impairment compared with patients in the highest tertile. Considering the association between CMBs and the tertiles of serum calcium, subjects in lowest tertile of serum calcium were associated with higher presence of CMBs ($P = 0.01$) and deep CMBs ($P = 0.02$), but not with strictly lobar CMBs (Table 2). However, relationships between the tertiles of serum calcium and CMBs or deep CMBs were no significant after adjusting for age, sex, smoking habits, drinking habits, and renal impairment ($P > 0.05$).

When serum calcium levels were dichotomized comparing the lowest tertile to all other categories, patients with serum calcium levels ≤2.15 mmol/L had higher presence of CMBs ($P = 0.005$, OR = 4.84, 95% CI 1.53–15.34) and higher risk of deep CMBs

Table 1

Baseline characteristics of ischemic stroke patients with AF/RHD with and without CMBs.

	with CMBs n = 39	without CMBs n = 28	*P*
Male, n (%)	19 (48.7)	9 (32.1)	0.18
Age, mean ± SD	69.85 ± 11.33	63.71 ± 12.14	0.04
Current smoking, n (%)	6 (15.4)	5 (17.9)	0.79
Alcohol intake, n (%)	4 (10.3)	6 (21.4)	0.21
Hypertension, n (%)	21 (53.8)	8 (28.6)	0.04
Diabete mellitus, n (%)	11 (28.2)	11 (39.3)	0.34
Renal impairment, n (%)	7 (17.9)	3 (10.7)	0.41
Previous TIA/stroke, n (%)	8 (20.5)	10 (35.7)	0.17
NIHSS on admission, mean ± SD	7.62 ± 5.86	10.82 ± 7.57	0.06
Total cholesterol (mmol/L), mean ± SD	4.08 ± 0.98	4.05 ± 0.98	0.90
TG (mmol/L), mean ± SD	1.56 ± 1.57	1.37 ± 0.80	0.56
HDL (mmol/L), mean ± SD	1.40 ± 0.36	1.34 ± 0.32	0.49
LDL (mmol/L), mean ± SD	2.29 ± 0.86	2.25 ± 0.80	0.86
Serum calcium (mmol/L), mean ± SD	2.20 ± 1.45	2.23 ± 0.79	0.31

AF = atrial fibrillation, CMBs = cerebral microbleeds, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NIHSS = National Institutes of Health Stroke scale, RHD = rheumatic heart disease, TG = triglycerides.

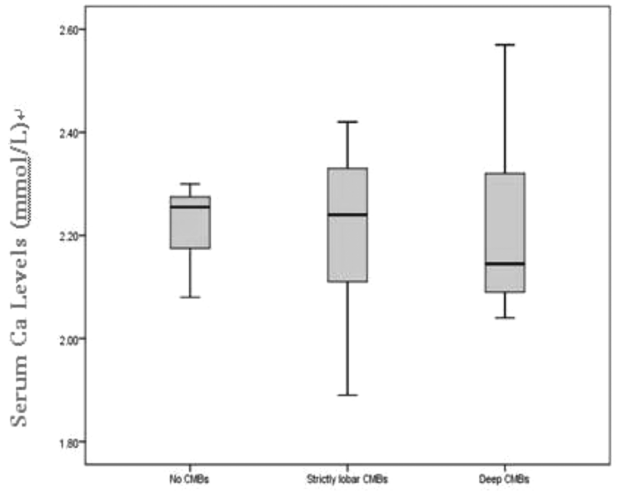

Figure 1. Distributions of Serum Ca levels according to CMB status.

($P = 0.006$, OR = 4.23, 95% CI 1.47–12.14) compared with those >2.15 mmol/L in the univariate *analysis*. When we adjusted for age, sex, smoking habits, drinking habits, and renal impairment, the presence of CMBs and deep CMBs was, respectively, 4.96- and 4.83-fold higher in patients with lower serum calcium levels (≤2.15 mmol/L) than in patients with higher serum calcium levels (Table 3).

4. Discussion

We found that lower levels of serum calcium (≤2.15 mmol/L) were independently associated with the presence of CMBs and deep CMBs in IS patients with AF and/ or RHD, but not with strictly lobar CMBs.

In the current study, we found the presence of CMBs was 58.2% in IS patients with AF and/or RHD, which is higher than the other studies reported (15–35%).[23–25] These differences may be due in part to ethnic and clinical differences among the patients in the study. Furthermore, we were careful to use only SWI, which is more sensitive at detecting CMBs than

Table 2

Distribution of demographic and clinical characteristics across different serum calcium tertiles.

	Tertile 1 (n = 25) (<2.15)	Tertile 2 (n = 21) (2.15–2.26)	Tertile 3 (n = 21) (>2.26)	*P*
Male, n (%)	13 (52.0)	8 (38.1)	7 (33.3)	0.41
Age, mean ± SD	72.32 ± 12.11	65.43 ± 11.45	63.14 ± 10.64	0.02
Current smoking, n (%)	6 (24.0)	4 (19.0)	1 (4.8)	0.20
Alcohol intake, n (%)	3 (12.0)	2 (9.5)	5 (23.8)	0.38
Hypertension, n (%)	15 (60.0)	6 (28.6)	138 (38.1)	0.09
Diabete Mellitus, n (%)	10 (40.0)	7 (33.3)	5 (23.8)	0.51
Renal impairment, n (%)	7 (28.0)	0 (0.0)	3 (14.3)	0.03
Previous TIA/stroke, n (%)	4 (16.0)	9 (42.9)	5 (23.8)	0.11
NIHSS on admission, mean ± SD	9.16 ± 6.23	8.62 ± 5.95	9.05 ± 8.30	0.96
Total cholesterol (mmol/L), mean ± SD	3.80 ± 1.07	4.27 ± 0.99	4.17 ± 0.79	0.22
TG (mmol/L), mean ± SD	1.17 ± 0.75	1.69 ± 1.69	1.64 ± 1.37	0.32
HDL (mmol/L), mean ± SD	1.30 ± 0.39	1.47 ± 0.26	1.37 ± 0.35	0.25
LDL (mmol/L), mean ± SD	2.12 ± 0.85	2.33 ± 0.89	2.39 ± 0.76	0.52
Presence of CMBs, n (%)	20 (80.0)	8 (38.1)	11 (52.4)	0.01
Strictly lobar CMBs, n (%)	5 (20.0)	4 (19.0)	4 (19.0)	1.00
Deep CMBs, n (%)	15 (60.0)	4 (19.0)	7 (33.3)	0.02

CMBs = cerebral microbleeds, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NIHSS = National Institutes of Health Stroke scale, TG = triglycerides.

Table 3

Multivariate relationships between CMBs and serum calcium levels.

	Low Hs-cTnT levels ≤2.15 mmol/L (n = 25)	High Hs-cTnT levels >2.15 mmol/L (n = 42)	
	P	OR	95% CI
Presence of CMBs	0.02	4.96	1.24–19.85
Strictly lobar CMBs, n (%)	0.88	0.88	0.18–4.38
Deep CMBs, n (%)	0.02	4.83	1.29–18.10

CMBs = cerebral microbleeds.

conventional T2*-weighted gradient-recalled echo imaging used in many previous studies.[23–25]

Although one cohort study[16] has shown that lower calcium intake and hypertension had joint effects on the risk of CMBs in healthy individuals, we provide preliminary evidence in a small cohort of Chinese IS patients with AF and/or RHD that lower serum calcium levels (≤2.15 mmol/L) were associated with presence of CMBs.

Three possible mechanisms may explain why low serum calcium levels are related to the presence of CMBs. First, low serum calcium levels might contribute to blood pressure elevation through inducing relaxation of isolated arteries by activating calcium receptors in perivascular nerves.[26] Second, calcium intake can reduce platelet aggregation and total cholesterol level.[27] Third, ionized calcium is an essential cofactor for the coagulation cascade, and plays an important role in the conversion of prothrombin to thrombin.[28] As the presence of CMBs is considered to be related with hypertension, hypercholesterolemia,[9] and hemostasis,[29] it is provable that the low serum calcium levels may have a synergistic effect on CMBs risk.

Our results indicate that lower serum calcium levels (≤2.15 mmol/L) are associated with presence of deep CMBs, but not with strictly lobar CMBs, providing insight into the potential role of calcium in CMBs. It is consistent with the previous study,[9] showing that classic markers of cardio or cerebrovascular disease had relationships with deep or infratentorial CMBs (hypertensive type) but not with strictly lobar CMBs (cerebral amyloid angiopathy type).

The present study has several limitations. Firstly, the study is a single-center, hospital-based study with a small, highly specific stroke patient population, which limited the extension of our conclusions. Larger, multicenter, and population-based studies are required to confirm our findings. Secondly, our study only focused on total serum calcium, whereas ionized calcium, the physiologically active compartment, was not measured. Furthermore, only a single serum calcium level admitted within 48 h was measured. The levels of serum calcium were impossible to remain unchanged after stroke, so the fluctuation of calcium levels during acute period might be better for clarifying whether there is an independent association between serum calcium levels and CMBs. Thirdly, The statistical power of our study was limited because of the fact that about 20% eligible patients were excluded for lacking serum calcium levels within 48 h after admission, so a prospective study in which serum calcium levels are measured systematically and repeatedly is needed. The study was performed in stroke patients with AF and/or RHD, so future study should determine whether the association between serum calcium levels and CMBs is involved with other types of stroke patients and the general population.

5. Conclusions

In conclusion, our results demonstrated that lower serum levels of calcium (≤2.15 mmol/L) are independently and significantly related to higher presence of CMBs in IS patients with AF and/ or RHD, especially among those with deep CMBs. Considering the small cohort included in the study, further studies are warranted to elucidate which accurate mechanism underlies the associations we found between the serum calcium levels and CMBs.

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