



Original Article

## Risk Factor Differences in Calcified and Non-Calcified Cervical Carotid Plaque

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### SUMMARY

**Background:** Vascular calcification is associated with the inflammatory process. Here, we investigated the relationship of serum lipoprotein-associated phospholipase A2 (Lp-PLA2) and traditional risk factors with carotid plaque calcification in patients with ischemic stroke (IS) or transient ischemic attack (TIA).

**Methods:** Patients with IS or TIA were divided into the calcification (Ca) and non-calcification (nCa) groups according to the results of the CTA of carotid artery with plaque. Lp-PLA2 level, demographics, vascular risk factors, and other clinical data were compared to analyze the risk factors for carotid plaque calcification.

**Results:** A total of 260 patients were enrolled, including 134 patients in Group Ca and 126 patients in Group nCa. Multiple logistic regression showed Lp-PLA2 ( $p = 0.016$ ), age ( $p = 0.010$ ), and diabetes ( $p = 0.010$ ) were independent risk factors of carotid artery plaque calcification. The Spearman's rank correlation coefficients showed Lp-PLA2 ( $r = 0.372$ ,  $p = 0.000$ ), age ( $r = 0.325$ ,  $p = 0.000$ ), and diabetes ( $r = 0.421$ ,  $p = 0.000$ ) had a positive correlation with the calcification of the carotid artery.

**Conclusions:** Serum Lp-PLA2, age, and diabetes were associated with carotid plaque calcification in patients with cerebral infarction or TIA. The inflammatory process mediated by Lp-PLA2 and diabetes may be involved in the pathogenesis of carotid calcification.

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## 1. Introduction

Carotid plaque calcification is an integral part of the active process of atherosclerosis, occurring in up to 60% of carotid atherosclerotic lesions.<sup>1</sup> Previous studies have shown that the formation, development, calcification, and rupture of atherosclerotic plaques are accompanied by inflammatory mediators.<sup>2,3</sup> Several studies have also shown that elevated levels of circulating inflammatory factors, such as lipoprotein-associated phospholipase A2 (Lp-PLA2) and interleukin-6 may be associated with atherosclerotic diseases.<sup>4,5</sup> Lp-PLA2 is a vascular inflammation marker involved in the different stages of atherosclerosis.<sup>6,7</sup> Although Lp-PLA2 has pro-atherosclerotic effects, its association with carotid atherosclerotic plaque calcification remains unclear. We postulated that carotid plaque calcification with morphological characteristics of a vulnerable plaque phenotype may have inflammation-related risk factors. In this study, a cross-sectional analysis was used to investigate the relationship between cardiovascular risk factors, serum Lp-PLA2, and carotid plaque calcification in patients with ischemic stroke (IS) or transient ischemic attack (TIA) for 1–6 months.

## 2. Materials and methods

### 2.1. Subjects

This study prospectively included patients with IS or TIA who were hospitalized in the Department of Neurology at Wuxi People's Hospital and underwent head CT from October 2016 to December 2017. The inclusion criteria were as follows: age  $\geq 18$  years, patients with non-cardiogenic ischemic stroke or TIA, and a time interval from onset to enrollment in this study ranging from 15 days to 6 months. The exclusion criteria were as follows: patients with cardiogenic stroke or cerebellar infarction, non-atherosclerotic stenosis of the carotid artery (e.g., radioactive, neoplastic, infective, arterial dissection); previous history of carotid stenting or endarterectomy; extent of calcification of cervical carotid artery  $>$  grade 3 (calcification  $270\text{--}360^\circ$  around the carotid circumference) or thickness of calcification of cervical carotid artery  $>$  grade 3 (calcification  $>$  3 mm thick); other serious comorbid conditions that may affect the level of calcification, such as chronic liver/kidney insufficiency/dialysis, hyperthyroidism/hyperparathyroidism, malignant tumors, metabolic disorders; recent infections such as fever, chronic inflammation, autoimmune diseases, and other diseases that may affect the level of inflammatory markers in the body; and recent history of bone fractures, administration of bisphosphonates or other treatments for osteoporosis. This study was reviewed and approved by the

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Ethics Committee of our institute, and all the subjects had signed the informed consent.

## 2.2. Data collection

Patients' demographics, cerebrovascular risk factors (SBP, DBP, history of smoking and drinking, diabetes, hypertension, hyperlipidemia, coronary heart disease and family history, and previous stroke/transient ischemic attack), drug use (antihypertensives, antiplatelet drugs, or statins), and results of clinical routine laboratory examination indices were collected and recorded.

## 2.3. ELISA

Blood samples were drawn from the antecubital vein after an overnight fast and were collected in ethylenediaminetetraacetic acid (EDTA) tubes. To reduce batch-to-batch and measurement errors, all of the specimens were tested in batches after the sampling was completed. The serum Lp-PLA2 concentration was measured by enzyme-linked immunosorbent assays (ELISAs) according to the manufacturer's instructions (Lp-PLA2 enzyme immunoassay kit, catalog number CSB-E08319h, CUSABIO company, USA). The participants were classified into 2 groups according to the quartile of the Lp-PLA2 concentration.

## 2.4. Definition of cerebrovascular risk factors

Traditional cerebrovascular risk factors were mainly obtained from blood sample tests and inquisition of patients' disease history as follows: 1) diabetes: fasting blood glucose  $\geq 7.0$  mmol/L (126 mg/dL), or taking oral hypoglycemic agents or insulin therapy; 2) high blood pressure SBP:  $\geq 140$  mmHg, or DBP  $\leq 90$  mmHg, or were using antihypertensive drugs; 3) hyperlipidemia: total cholesterol  $\geq 5.7$  mmol/L (240 mg/dL), or total triglyceride  $\geq 1.7$  mmol/L (150 mg/dL), or with history of hyperlipidemia in private prosecution, or were using lipid-lowering drugs; 4) history of smoking and drinking: with current or previous history of smoking and drinking; 5) family history of cardiovascular and cerebrovascular diseases: with first-degree relatives diagnosed as atherosclerotic coronary or cerebral artery disease (male  $\geq 55$  years old, female  $\geq 60$  years old); 6) Hyperhomocysteinemia  $\geq 10$   $\mu\text{mol/L}$ ; 7) obesity: BMI  $\geq 30$  kg/m<sup>2</sup>.

## 2.5. Analysis and quantitation of cervical carotid artery plaque calcification

Computed tomography (CT) scans were performed using a dual source CT (Somatoma Definition, Siemens Medical Solutions, Forchheim, Siemens, Germany) similarly to previous studies.<sup>8</sup> Patients with plaque calcification found anywhere within the assessed vessel segment were included in Group Ca; otherwise, the patients were included in Group nCa. Quantitative analysis of carotid plaque calcification was performed using the Agatston method.<sup>9</sup> Quantitative calcification analysis was performed using the machine-adapted calcification integration software (Syngo Calcium Scorings, Siemens, Forchheim, Germany). The calcification scores of all subjects were calculated by skilled imaging specialists who were blinded to the study design.

## 2.6. Analysis of cervical carotid artery stenosis and degree of circumferential calcification

Carotid arteries within the above-mentioned vessel segment

were also included in the analysis of stenosis. The percentage of carotid artery stenosis was based on the standards of North American Symptomatic Carotid Endarterectomy (NASCET).<sup>10</sup> In this study, the study subjects were divided into two categories, namely mild or moderate/severe stenosis, for statistical analysis. The degree of circumferential calcification and thickness of calcification were graded for the cervical carotid arteries on the basis of the CT findings as previously reported.<sup>11</sup> The extent of the cervical carotid artery calcification was graded into 4 levels. The degree of calcification was classified as Grade 0 (showing no calcification), 1 (showing a dot of calcification), 2 (showing crescentic area of calcification  $< 90^\circ$  of carotid wall circumference), 3 (showing calcification from  $90^\circ$ – $270^\circ$  degrees circumference), or 4 (showing calcification  $270^\circ$ – $360^\circ$  around carotid circumference). The thickness of the cervical carotid artery calcification was also graded into 4 levels: Grade 0 (no calcification), 1 (1-mm-thick calcification), 2 (2-mm-thick calcification), or 3 (3-mm-thick calcification), 4 ( $> 3$ -mm-thick calcification).

## 2.7. Statistical analysis

The numerical variables were expressed as mean  $\pm$  standard deviation (normal continuous distribution data) or median (interquartile range) (non-normal data); categorical variables were expressed as frequency (%). In univariate comparison, categorical variables used the Pearson's  $\chi^2$  test or Fisher's exact test. Non-parametric data were tested with the Mann-Whitney U test. Normal continuous distribution data were analyzed using the independent sample t test. The factors with  $p < 0.1$  in the univariate test were set as independent variables, together with calcification as the independent variable (calcification was assigned to 1, and no calcification was assigned to 0), for the multivariate binary logistic regression analysis. Relative risks were calculated using the adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate logistic regression analysis was used to determine the risk factors for carotid plaque calcification. The Spearman rank correlation test was used to analyze the association of age, diabetes, and serum Lp-PLA2 levels with carotid calcification scores, with bilateral  $p < 0.05$  considered as statistical significant. All statistical analyses were performed using the statistical software SPSS 20.0.

## 3. Results

### 3.1. Basic composition

A total of 289 patients with non-cardiogenic IS or TIA in the anterior circulation within 15 days to 6 months of the study had undergone head and neck vascular CTA, among whom 12 patients were excluded from the study due to the history of carotid stenting, 7 patients because of hepatic and renal insufficiency, 3 patients because of hyperthyroidism, 5 patients because of pneumonia, and 2 patients because of autoimmune diseases. Finally, 260 patients were included, with an average age of  $63.8 \pm 5.6$  years, and the ratio of males accounting for about 57.4%, including IS and TIA patients accounting for 92% and 8%, respectively, of the total number of patients. Furthermore, 134 patients were divided into groups Ca and nCa consisted of 134 and 126 patients, respectively.

### 3.2. Univariate comparison

The difference in median age was statistically significant ( $p < 0.05$ ). Patients with diabetic differences were statistically significant ( $p < 0.05$ ). The median level of Lp-PLA2 in Group Ca was statistically

higher than that in Group nCa ( $p < 0.05$ ). Other cardiovascular risk factors showed no statistical differences between the two groups ( $p \geq 0.05$ ) (Table 1).

### 3.3. Multivariate logistic regression analysis

The variables with  $p$  values  $< 0.1$  in the univariate comparison, namely the age, serum Lp-PLA2, diabetes, fasting blood glucose, and possible risk factors reported previously (such as hypertension or moderate-severe stenosis), were set as the independent variables, whereas calcification was the dependent variable (calcification was assigned to 1 and no calcification was assigned to 0), for the multivariate binary logistic regression analysis. After correcting the confounding factors, such as fasting blood glucose, hypertension, or moderate-severe stenosis, the multivariate logistic regression analysis showed that age (OR: 1.053, 95% CI: 1.013–1.095,  $p = 0.010$ ), Lp-PLA2 (OR: 1.312, 95% CI: 1.033–1.623,  $p = 0.016$ ), and DM (OR: 2.513, 95% CI: 2.053–3.423,  $p = 0.010$ ) were the independent correlative factors for carotid plaque calcification (Table 2).

### 3.4. Analysis of spearman rank correlation test

The Spearman rank correlation test revealed that age ( $r = 0.325$ ,  $p = 0.000$ ), serum Lp-PLA2 ( $r = 0.372$ ,  $p = 0.000$ ), and DM ( $r = 0.421$ ,  $p = 0.000$ ) were positively correlated with the carotid calcification score (Table 3).

## 4. Discussions

The results of this study revealed that age, diabetes, and Lp-PLA2 were independently and positively correlated with carotid plaque calcification in patients with IS or TIA. However, no significant difference was found in the comparison of other traditional risk factors.

Interestingly, Lp-PLA2 was found to be positively correlated with

mild or moderate carotid calcification in this study. In the CARDIA study, an independent association was found for Lp-PLA2 mass with calcified coronary plaque among young adults.<sup>12</sup> Lp-PLA2 has been confirmed to be correlated with cardiac and cerebral ischemic events and atherosclerotic progression.<sup>13</sup> It is believed that Lp-PLA2 can catalyze the products of the pro-inflammatory process for the initiation, formation, development, and plaque rupture of atherosclerosis.<sup>14</sup> Inflammation has been considered to be an important factor in promoting the progression of atherosclerosis and may also initially activate plaque calcification.<sup>15</sup> Abdelbaky et al. showed that inflammation occurs prior to calcification.<sup>16</sup> In the early stages of atherosclerosis, vascular inflammation may initiate calcium deposition and eventually lead to the formation of microcalcification nuclei, thus further inducing inflammation and calcium deposition.<sup>17</sup> Locally, Lp-PLA2 has been detected in human carotid atherosclerotic plaques, but not in areas of the adjacent normal arterial wall.<sup>18</sup> Its expression is mainly confined to plaque areas with massive lipid accumulation and leucocyte infiltration, cellular necrosis, and calcification.

**Table 2**  
Multivariate Binary Logistic Regression Analysis between two groups.

Item	B	S.E	OR	95%CI	$p$
Age	0.042	0.030	1.053	1.013–1.195	0.010
DM	2.017	0.115	2.182	2.054–3.381	0.010
Lp-PLA2	0.193	0.082	1.312	1.033–1.623	0.016
FBG	-0.018	0.134	0.941	0.234–1.271	0.876
Hypertension	0.212	0.433	1.223	0.517–2.904	0.654
Moderate/severe stenosis	0.293	0.067	0.909	0.204–0.556	0.343

**Table 3**  
Spearman rank correlation test of carotid artery calcification related factors.

Item	Age	DM	Lp-PLA2	FBG	Hypertension	Moderate/severe stenosis
R	0.325	0.421	0.372	0.095	0.065	0.050
$p$	0.000	0.000	0.000	0.281	0.254	0.310

**Table 1**  
Comparison of demographic and clinical data between two groups.

Item	Ca (n = 134)	nCa (n = 126)	T/Z/ $\chi^2$	$p$
Age [years, M (IQR)]	65 (55,88)	53 (51,67)	-4.348	0.000
Male (n, %)	77 (57.4)	73 (57.9)	0.006	0.938
BMI [ $\text{kg}/\text{m}^2$ , M (IQR)]	24.2 (22.4,26.8)	23.1 (21.2,27.3)	-0.532	0.667
SBP [mmHg, M (IQR)]	134 (115,146)	126 (123,144)	-0.763	0.388
DBP [mmHg, M (IQR)]	80 (74,89)	75 (72,88)	-0.670	0.539
Smoking (n, %)	60 (44.7)	52 (41.2)	0.198	0.656
Drinking (n, %)	44 (32.8)	36 (28.5)	0.372	0.542
Hypertension (n, %)	67 (46.5)	54 (42.9)	0.233	0.630
Hyperlipidemia (n, %)	52 (38.8)	43 (34.1)	0.428	0.513
DM (n, %)	53 (39.6)	22 (17.7)	13.819	0.000
Moderate/severe stenosis (n, %)	36 (26.9)	27 (21.4)	0.770	0.380
IS/TIA (n, %)	42 (31.3)	33 (26.2)	0.608	0.436
Ischemic heart disease (n, %)	22 (16.4)	15 (11.9)	0.745	0.388
Lp-PLA2 [ng/L, M (IQR)]	316.2 (103.5–456.8)	159.4 (73.0–312.9)	6.327	0.000
Hcy [ $\mu\text{mol}/\text{L}$ , M (IQR)]	8.4 (4.2,15.6)	6.9 (6.5,12.3)	-1.132	0.263
WBC [ $\times 10^9$ , M (IQR)]	5.9 (5.1,6.7)	6.3 (5.2,7.5)	-1.264	0.149
CRP [mg/L, M (IQR)]	2.9 (0.5–7.8)	1.6 (0.0,5.5)	1.126	0.302
FBG [mmol/L, M (IQR)]	4.7 (4.5,7.6)	4.5 (4.4,6.1)	-1.729	0.058
TC [mmol/L, M (IQR)]	4.19 (0.92,5.80)	3.49 (0.95,4.82)	-0.022	0.875
TG [mmol/L, M (IQR)]	1.32 (0.90,2.86)	1.46 (1.16,1.83)	-1.296	0.242
LDL [mmol/L, M (IQR)]	2.33 (1.32,3.89)	2.18 (1.74,3.81)	-0.749	0.226
HDL [mmol/L, M (IQR)]	1.13 (0.91,1.59)	1.18 (0.83,1.41)	-0.427	0.548
Medication (n, %)				
Antihypertensive drugs	65 (48.5)	50 (39.7)	1.708	0.191
Antiplatelet drugs	61 (45.5)	55 (43.7)	0.032	0.858
Stains	53 (39.6)	45 (35.8)	0.260	0.610

Calcification has been proposed as a stabilizing factor rather than a risk factor for carotid plaque instability by some researchers; however, the results of the present study and that of other researchers lead to different conclusions. The relevance of atherosclerotic plaque calcification to plaque structural stability has been investigated most commonly in the coronary arteries.<sup>19,20</sup> The relationship between the amount of calcium involvement and plaque vulnerability has not yet been extensively evaluated in carotid plaque. Eisenmenger et al.<sup>21</sup> investigated the grade of carotid calcification by CT angiography and identified a high correlation with intraplaque hemorrhage. Collett et al.<sup>22</sup> analyzed the correlation of calcification with neoangiogenesis within the plaque and demonstrated a direct correlation between spot calcification and micro-vascularization. Baradaran et al.<sup>23</sup> reported that calcified plaque was negatively associated with downstream ischemic events; however, the systematic review was biased by a significant level of heterogeneity in the calcification evaluation. Van den Bouwhuisen et al.<sup>24</sup> analyzed 329 carotid specimens and identified a correlation between carotid calcification and intraplaque hemorrhage from the Rotterdam study data; the authors concluded that different types of calcification are possible, and some of them are more frequently associated with plaque hemorrhage compared with others. Biologically, the relationship between calcification and clinical events likely relates to mechanical instability introduced by calcified plaque at its interface with softer, noncalcified plaque. In general, as calcification progresses, the interface surface area increases initially, but eventually decreases as plaques coalesce. Based on the considerations of the morphological characteristics and calcium dose-dependent risk of plaque rupture, this study excluded cases with high-grade calcification with an extent of cervical carotid artery calcification > grade 3 or cervical carotid artery calcification thickness > grade 3. This category of carotid plaques with high grade calcification may be more biomechanically stable and less prone to disruption. It is one of the reasons that a high level of serum Lp-PLA2 was found to be positively correlated with the carotid calcification in the study. Giving all these premises, a mild or moderate level of carotid calcification cannot be considered an element of plaque stability. Finally, Lp-PLA2 may reflect a systemic state of vulnerable atherosclerosis without localizing the real culprit lesion. A multi-marker strategy that coupled serum biology and imaging techniques, such as contrast ultrasound, high-resolution MRI, and nuclear imaging to analyze parameters of instability could improve the identification of high-risk symptomatic atherosclerotic lesions to guide further effective therapy.

This study confirmed that age was a high-risk factor for carotid calcification and was consistent with previous findings that age (older than 65 years) is associated with carotid calcification. With aging, plaques gradually progress toward calcification, and calcification becomes more common in the aorta, coronary artery, carotid artery, and peripheral artery. This study did not find the impact of risk factors in other cardiovascular and cerebrovascular diseases, such as hypertension and hyperlipidemia, on calcification, and it may be related to the different groups of the enrolled patients. At the same time, studies have shown that although there are crosses between the risk factors of coronary artery and carotid artery atherosclerosis, the risk factors of these two diseases are not exactly the same,<sup>25,26</sup> indicating that initiation factors and mechanism of occurrence of calcification are also not exactly the same.

This study also indicated that diabetes is a risk factor for carotid artery calcification. The relationship between diabetes and carotid calcification has been demonstrated by several studies. Studies have shown that vascular calcification is widespread in diabetic patients,

including intimal calcification and medial calcification, and the arterial calcification index in diabetic patients is significantly higher than that in non-diabetic patients.<sup>27–29</sup> The exact mechanism of vascular calcification in diabetics is not fully understood at present. It may be a cell-mediated active regulatory process involving many factors that promote and inhibit calcification, such as hyperglycemia, insulin resistance, kidney disease, inflammation, or abnormal expressions of bone-related proteins.<sup>30</sup>

This study has some limitations: (1) the study had a small sample size; however, the data may serve as a pilot study for future large scale prospective studies comparing differences in the relation between Lp-PLA2 and carotid calcification; (2) the patients were enrolled from a single center; (3) the observational and cross-sectional nature of the data, precluding causal inferences; (4) the vast majority of these patients were characterized by anterior circulation infarction, and patients with high-grade carotid calcification were excluded. There was a certain bias in the inclusion of these cases.

In summary, this study suggested that the significance of old age, diabetes, and serum Lp-PLA2 toward risk factor stratification of carotid plaque calcification should be further investigated. Regardless of the pathophysiological mechanism behind this association, the findings strengthen the role of carotid artery calcification assessment in the routine management of older symptomatic patients with high serum Lp-PLA2 level or DM.

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## Disclosure of conflict of interest

None.

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