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ORIGINAL RESEARCH

Relationship Between Serum Lipid Profiles and Carotid Intraplaque Neovascularization in a High–Stroke-Risk Population: A Cross-Sectional Study in China

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BACKGROUND: Evidence of the association between serum lipid profiles and intraplaque neovascularization (IPN) is still limited. We aimed to study the value of a novel Doppler method, superb microvascular imaging, in correlating serum lipid profiles and evidence of IPN in a population with a high risk of stroke.

METHODS AND RESULTS: A community-based cross-sectional study was conducted in Beijing, China. Residents (aged ≥40 years) underwent questionnaire interviews, physical examinations, and laboratory testing in 2018 and 2019. Subjects with a high risk of stroke were then selected. Standard carotid ultrasound and carotid plaque superb microvascular imaging examinations were then performed on the high–stroke-risk participants. Logistic regression was used to evaluate the relationship between serum lipid profiles and carotid plaque IPN. Overall, a total of 250 individuals (mean age, 67.20±8.12 years; 66.4% men) met the study inclusion criteria. Superb microvascular imaging revealed carotid plaque IPN in 96 subjects (38.4%). Subjects with IPN were more likely to be current smokers (34.0% versus 46.9%, P=0.046), and their identified carotid plaques were much thicker (2.35±0.63 mm versus 2.75±0.80 mm, P=0.001). Serum lipids, including total cholesterol, non–high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were positively associated with the presence of IPN (4.33±1.00 mmol/L versus 4.79±1.12 mmol/L, P=0.001; 2.96±0.92 mmol/L versus 3.40±1.01 mmol/L, P=0.001; 2.18±0.76 mmol/L versus 2.46±0.80 mmol/L, P=0.005, respectively), and after adjustment for other confounders, the positive relationship remained significant. Furthermore, non–high-density lipoprotein cholesterol (odds ratio, 2.62 [95% CI, 1.35–5.06]) was significantly associated with the presence of carotid plaque IPN even after adjusting for low-density lipoprotein cholesterol.

CONCLUSIONS: Total cholesterol, non–high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were positively associated with the presence of carotid IPN in a Chinese high–stroke-risk population. Further prospective studies should be conducted to better understand how much finding IPN adds to current stroke prediction tools.

Key Words: intraplaque neovascularization ■ lipids ■ stroke ■ superb microvascular imaging ■ ultrasonography

Stroke is among the major causes of mortality and disabilities in the world.[1] In China, with over 2 million new cases annually, stroke is associated with the highest disability loss of any disease.[2] Plaque vulnerability is increasingly recognized as a driver of lesion rupture and risk for stroke.[3] Recently, the role of intraplaque neovascularization (IPN) as a feature of plaque vulnerability has gained serious interest.[4] Studies have confirmed a pronounced association between IPN and plaque vulnerability in terms of increased risk for neovessel rupture, hemorrhage, and inflammation, which are evident markers of stroke and

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For Sources of Funding and Disclosures, see page 6.

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CLINICAL PERSPECTIVE

What Is New?

- This study confirms that a novel Doppler method, superb microvascular imaging, was effective for carotid intraplaque neovascularization (IPN) detection.
- The relationship of serum lipid profiles and the evidence for IPN in a population with a high risk of stroke was explored.
- Total cholesterol, non–high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were positively associated with the presence of carotid IPN in a Chinese high–stroke-risk population.

What Are the Clinical Implications?

- Superb microvascular imaging should be considered for IPN detection in populations at high risk of stroke.
- In hyperlipidemia populations, carotid plaque IPN should be a concern.
- Non–high-density lipoprotein cholesterol may play an important role in neovascularization.

Nonstandard Abbreviations and Acronyms

IPN	intraplaque neovascularization
SMI	superb microvascular imaging
TC	total cholesterol

cardiovascular events.[5–8] It would be of great importance to prevent stroke early by detecting and intervening in IPN, and it has inspired the development of noninvasive imaging technologies with the objective of visualizing the IPN in the carotid plaque. Superb microvascular imaging (SMI) is a novel Doppler technique that can detect subtle and slow-flow signals to enable the visualization of intraplaque microvascular flow without contrast media.[9] Several studies have demonstrated that SMI is efficient for the detection of carotid plaque IPN that is verified by histology.[10–12] Previous work from our team found an association of SMI-detected IPN and clinical history of stroke or transient ischemic attack among a high–stroke-risk population.[13] Previous studies reported that serum lipids, including triglycerides, total cholesterol (TC), non–high-density lipoprotein cholesterol (non–HDL-C), and low-density lipoprotein cholesterol (LDL-C), are positively associated with the presence of carotid plaques in White and Asian populations.[14–18] However, whether serum lipid profiles are related to the carotid plaque IPN has never been investigated.

Therefore, the present cross-sectional study was performed to study the value of the novel Doppler method, SMI, in correlating serum lipid profiles and the evidence of carotid plaque IPN in a population with a high risk of stroke in China.

METHODS

Data Availability

The data sets used or analyzed in the current study are available from the corresponding author on reasonable request.

Ethics Statement

The Ethics Committee of the China National Stroke Screening Survey, including key neurologists, cardiologists, and epidemiologists, was established to provide ethical approval and technical support to the program. Written informed consent was obtained from each participant.

Study Sample

The study was conducted in 2018 and 2019 among residential dwellers who were continuous community residents in the Dongcheng District, Beijing, China. Each person was screened for the following 8 risk factors: (1) blood pressure ≥140/90 mm Hg; (2) atrial fibrillation or valvular heart disease, where atrial fibrillation was defined for an individual with a history of atrial fibrillation diagnosed by clinicians or for those who were screened by resting 12-lead electrocardiogram; (3) smoking status; (4) dyslipidemia (triglycerides ≥2.26 mmol/L, TC ≥6.22 mmol/L, LDL-C ≥4.14 mmol/L, or HDL-C <1.04 mml/L); (5) diabetes, defined according to the 1999 World Health Organization criteria; (6) lack of exercise, defined as exercise <3 times per week and <30 minutes each time; (7) body mass index ≥26, calculated as body weight in kilograms divided by body height squared in meters; and (8) family history of stroke.

Venous blood samples were obtained after an overnight fast of at least 8 hours. All blood samples were analyzed in a national central laboratory in Beijing using the Olympus autoanalyzer 2700 (Olympus Instruments, Tokyo, Japan) with strict quality control. Triglycerides were measured by the glycerol lipase oxidase glycerol phosphate oxidase-peroxidase anti peroxidase complex method (Kyowa Medex, Tokyo, Japan). LDL-C and HDL-C concentrations were measured enzymatically (Kyowa Medex).

For individuals who had at least 3 stroke risk factors, standard carotid ultrasound was performed to detected carotid artery plaque burden. If carotid plaque was detected, the carotid plaque SMI examination was performed to observe the IPN.

Finally, a total of 250 samples with completed carotid SMI ultrasound examinations were included in this study.

Standard Ultrasound and SMI Examinations

All ultrasound scans were conducted with a high-resolution ultrasound system (Aplio 500 UZRI-A500A; Canon Medical Systems, Tokyo, Japan) equipped with a 7.5-MHz linear probe (Aplio PLT-704SBT; Canon Medical Systems). Carotid plaques were defined as focal regions with a thickness ≥1.5 mm. In cases of individuals with >1 unique plaque, only the thickest plaque was included in our analysis. The scan of every plaque was conducted under both longitudinal and transverse sections. Stenosis severity was assessed using the criteria of the Society of Radiologists in Ultrasound. In short, a peak systolic velocity of 125 to 230 cm/s was considered to indicate 50% to 69% stenosis, and a lesion and a peak systolic velocity of 230 cm/s was considered to indicate ≥70% stenosis; no detectable patent lumen and no flow on color Doppler were considered to indicate total occlusion.

For SMI examination, SMI mode was switched, and the region of interest was positioned to include the entire plaque. The following conditions, including velocity range, frame rate, mechanical index, and dynamic range, was set.[18] Neovascularization was identified by short-line or stripe-like hyperintense echoes as shown in Figure 1.

Four experienced radiologists performed all of the routine ultrasound scans. Two independent radiologists (Y.W. and L.Z.) who have >6 years of experience in ultrasound performed the SMI scans. A senior radiologist (H.Y.W.) who has >10 years of experience in ultrasound was consulted if any disagreement occurred until an agreement was reached. All radiologists were blinded to the participant histories.

Statistical Analysis

Quantitative data are presented as the mean±SD. Qualitative data are presented as frequency. A χ^2 test or Fisher exact test was applied to categorical variables, whereas an independent *t* test was used to compare continuous variables. The correlation between IPN and the stroke risk factors we tested were analyzed. First, univariate regression analysis was done, and 2 significant variables, current smoker and plaque thickness ($P<0.05$), were selected. Then, the 2 variables were put into binary logistic regression. $P<0.05$ was considered significant for all tests. The κ value was calculated to assess interobserver variability. The statistical analyses were performed using SPSS (version 19.0; IBM, Armonk, NY) software. The power of the study was calculated via PASS 11(NCSS, Kaysville, UT).

RESULTS

Participants' Baseline Characteristics

The baseline characteristics of the study subjects are listed in Table 1. Among the 250 subjects, the mean

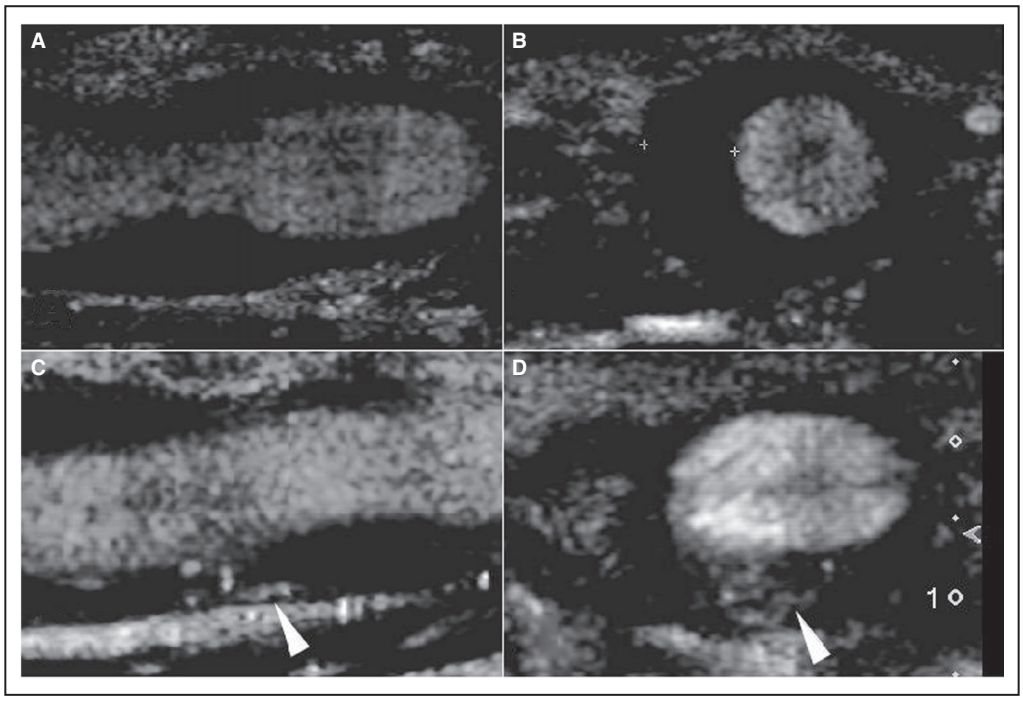

Figure 1. No intraplaque neovascularization (IPN) on longitudinal and transverse sections of plaque (A and B) and IPN on longitudinal and transverse sections of plaque (C and D).

Table 1. Baseline Characteristics of All Subjects (n=250)

Risk factors	Value
Age, y	67.20±8.12
Male sex	166 (66.4)
BMI, kg/m^2	25.71±3.98
Hypertension	208 (83.2)
Diabetes	127 (50.8)
Current or former smoking	118 (47.2)
Current smoking	97 (38.8)
Lack of exercise	89 (35.6)
Atrial fibrillation or valvular heart disease	15 (6.0)
Lipids, mmol/L	
TC	4.51±1.07
Triglycerides	1.78±0.92
LDL-C	2.29±0.79
HDL-C	1.38±0.36
Non–HDL-C	3.13±0.98
Homocysteine	15.00±8.30
Use of drugs	
Antihypertensive medication	172 (68.8)
Statins	123 (49.2)
Diabetes medication	100 (40)
Antithrombotic medications	10 (4.0)

BMI indicates body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and TC, total cholesterol.

age was 67.20±8.12 years, and 66.4% were men. The number of subjects who had stroke risk factors including hypertension, diabetes, smoking status, lack of exercise, and atrial fibrillation were 208 (83.2%), 127 (50.8%), 118 (47.2%), 89 (35.6%), and 15 (6.0%), respectively. Medications used included antihypertensive medications in 172 (68.8%) subjects, statins in 123 subjects (49.2%), diabetes medications in 100 (40.0%) subjects, and antithrombotic medications in 10 (4.0%) subjects. Plaque characterization by standard and SMI ultrasound are listed in Table 2. Among the 250 subjects, 240 (96.0%), 7 (2.8%), and 3 (1.2%) individuals had <50%, 50% to 69%, and ≥70% carotid stenosis, respectively. The mean value of maximum plaque thickness was 2.50±0.73 mm; 75 (30%) plaques had inhomogeneous texture and 16 (6.4%) had irregular plaque surface. SMI revealed no IPN in 154 subjects (61.6%) and IPN in 96 subjects (38.4%).

Factors Associated With the Presence of Neovascularization

As shown in Table 3, compared with subjects without IPN, subjects with IPN were more likely to be current smokers (34.0% versus 46.9%, *P*=0.046), and their identified carotid plaques were much thicker (2.35±0.63 mm versus 2.75±0.80 mm, *P*=0.001). The presence of IPN was not associated with hypertension,

Table 2. Plaque Characterization by Standard and SMI Ultrasound

Carotid ultrasound findings	Value
Carotid stenosis degree	
Stenosis <50%	240 (96)
Stenosis 50%–69%	7 (2.8)
Stenosis ≥70%	3 (1.2)
Standard ultrasound mode	
Max plaque thickness, mm	2.50±0.73
Inhomogeneous plaque texture	75 (30)
Irregular plaque surface	16 (6.4)
SMI mode	
IPN on SMI	96 (38.4)

IPN indicates intraplaque neovascularization; and SMI, superb microvascular imaging.

atrial fibrillation or valvular heart disease, diabetes, lack of exercise, body mass index, and family history of stroke.

Associations of Serum Lipid Profiles With IPN

As seen in Table 3, the serum lipid profiles, including TC, LDL-C, and non–HDL-C, were positively and significantly associated with the presence of IPN (4.33±1.00 mmol/L versus 4.79±1.12 mmol/L, *P*=0.001; 2.18±0.76 mmol/l versus 2.46±0.80 mmol/L, *P*=0.005; 2.96±0.92 mmol/L versus 3.40±1.01 mmol/L, *P*=0.001, respectively).

Logistic regression models were constructed to evaluate the independent effects of TC, LDL-C, and non–HDL-C on carotid plaque IPN. In the fully adjusted model (current smoking and plaque thickness), continuous TC (odds ratio [OR], 1.58 [95% CI, 1.22–2.06]), LDL-C (OR, 1.63 [95% CI, 1.15–2.32]), and non–HDL-C (OR, 1.82 [95% CI, 1.28–2.31]) were significantly associated with carotid plaque IPN, as seen in Figure 2. Additionally, in the fully adjusted model, for each additional unit of TC, LDL-C, and non–HDL-C, the chance of having carotid plaque IPN increased by 55% (OR, 1.58 [95% CI, 1.22–2.06]), 63% (OR, 1.63 [95% CI, 1.15–2.32]), and 72% (OR, 1.72 [95% CI, 1.28–2.31]), respectively.

In the mutually adjusted models, non–HDL-C (OR, 2.62 [95% CI, 1.35–5.06]) was positively and significantly associated with the presence of carotid plaque IPN, even after adjusting for LDL-C. However, LDL-C was no longer significantly associated with carotid plaques after adjusting for non–HDL-C (OR, 0.57 [95% CI, 0.25–1.23).

The Effect of Taking Statins on IPN

Among 198 patients with dyslipidemia, 123 (62.1%) individuals had taken statins. Compared with individuals taking statins, a larger percentage of those who have

Table 3. IPN on Superb Microvascular Imaging and Its Association With Clinical Characteristics

	IPN		
	No, n=154	Yes, n=96	*P* value
Risk factors			
Age, y	66.81±7.79	67.81±8.62	0.344
Male sex	98 (63.6)	68 (70.8)	0.15
BMI, kg/m^2	25.74±4.29	25.67±3.44	0.889
Hypertension	130 (84.4)	78 (81.3)	0.314
Diabetes	80 (51.9)	47 (49)	0.371
Current or former smoking	66 (42.9)	54 (56.3)	0.051
Current smoking	52 (34.0)	45 (46.9)	0.046*
Lack of exercise	57 (37)	32 (33.3)	0.589
Overweight or obese	33 (21.4)	21 (21.9)	0.527
Atrial fibrillation or valvular heart disease	9 (5.8)	6 (6.3)	0.549
Family history of stroke	69 (44.8)	31 (32.3)	0.063
Homocysteine	15.08±8.83	14.88±7.40	0.853
Lipids, mmol/L			
TC	4.33±1.00	4.79±1.12	0.001*
Triglycerides	1.77±0.96	1.78±0.84	0.958
LDL-C	2.18±0.76	2.46±0.80	0.005*
HDL-C	1.37±0.38	1.39±0.33	0.695
Non–HDL-C	2.96±0.92	3.40±1.01	0.001*
Max plaque thickness, mm	2.35±0.63	2.75±0.80	0.001*

BMI indicates body mass index; IPN, intraplaque neovascularization; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and TC, total cholesterol.

*indicates significant difference.

not have taken statins have IPN (49.3% versus 32.5%, *P*=0.024).

Reproducibility of SMI Findings

To establish the reproducibility of our qualitative assessment, intraobserver and interobserver agreement was determined by applying Cohen's κ statistic to the IPN grading by 2 different readers and by 1 reader at an interval of >7 days using video loops of SMI. Intraobserver and interobserver agreement for κ coefficient was good at 0.82 (95% CI, 0.78–0.87) and 0.76 (95% CI, 0.72–0.80), respectively.

DISCUSSION

The occurrence of stroke is closely related to the stability of carotid artery plaques, and identifying these vulnerable plaques is of critical significance. Imaging methods can be used to judge this stability. According to the latest version of the American Society of Echocardiography guidelines, the ultrasonic characteristics of carotid plaques, especially IPN, are an important basis for cardiovascular disease risk stratification.[19] IPN could be a cause of plaque instability through their rupture and the progression of intraplaque hemorrhage.[10–12] This may further cause an expansion of the plaque and abrupt occlusion of the involved artery.[20] In our study, we used a novel ultrasound technique, SMI, which could clearly detect carotid IPN at low speeds.

Lipid metabolism disorders have been shown to be strongly related to the development of atherosclerosis.[21] Previous studies have investigated the relationship between serum lipid profiles and the presence of carotid plaques in different populations. The result showed that TC, LDL-C, and non–HDL-C were suggested to be strongly associated with the presence of carotid plaques in a general population.[14,22,23] In our study, the findings indicate that increased TC, LDL-C, and non–HDL-C are related to an elevated chance of having carotid plaque IPN in a Chinese population with a high risk of stroke, and after adjustment for confounders, the positive relationship remained significant. The results indicate that dyslipidemia may affect

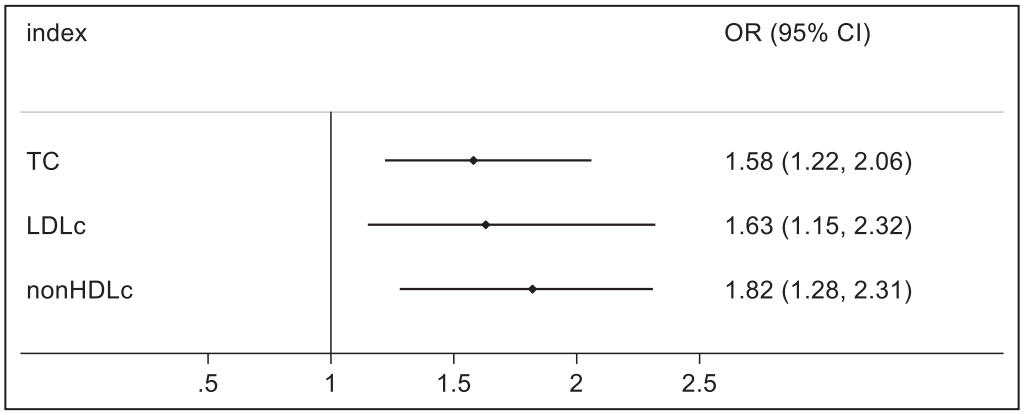

Figure 2. Forest plot of TC, LDLc, and nonHDLc (OR and 95% CI).
LDLc indicates low-density lipoprotein cholesterol; nonHDLc, non–high-density lipoprotein cholesterol; OR, odds ratio; and TC, total cholesterol.

not only plaque formation, but also neovascularization in plaque. IPN is a complex procedure that depends on the interaction of many antiangiogenic factors.[24] Vascular endothelial growth factor is one of the most well-recognized angiogenic factors.[25] Plasma vascular endothelial growth factor levels are elevated in patients with hyperlipidemia. Recent studies have found that lowering blood lipids can increase plaque stability and reduce plaque neovascularization. A cohort study showed a positive role of lipid-lowering treatment in coronary atherosclerosis regression, and the extent of coronary plaque regression was also positively associated with non–HDL-C reduction.[26] Additionally, Koutouzis et al indicated that statin therapy is associated with reduced IPN in the carotid arteries.[27] In this study, we found the same result as that in individuals taking statins, and a lower percentage of IPN was found (32.5% versus 49.3%, P=0.024).

In our study, the mutually adjusted models indicate that other components of non–HDL-C beyond LDL-C might contribute more to carotid plaque IPN. Consistent with our results, previous studies have demonstrated that apolipoprotein B, a major component of non–HDL-C but not LDL-C, was associated with the progression of carotid plaques or the risk of coronary heart disease.[28,29]

In this study, a positive relationship was observed between current smoking and the presence of carotid plaque IPN. Cigarette smoking is a known independent risk factor for the development of stroke. Evidence from previous epidemiological and clinical studies has shown that smoking is a risk factor for stroke.[30–32] Several mechanisms, including inflammation, atherosclerosis, and increased platelet aggregation have been associated with the development of stroke and cigarette smoking.[30,33,34] In a prospective cohort study of 22 071 US male physicians followed up for an average of 9.7 years, investigators found that current but not former cigarette smoking was significantly associated with an increased risk for stroke in men. Compared with those who never smoked, physicians currently smoking ≥20 cigarettes per day had relative risks of 2.71 and 1.46 for total nonfatal and fatal stroke, respectively, after adjusting for risk factors for stroke, which is consistent with our results.[35] It has been reported that plaque thickness is an important factor for stroke, as it is positively related to artery stenosis, which is an important indicator for stroke monitoring.[36] In our study, we found that the identified carotid plaques of subjects with IPN were much thicker.

The present study had some limitations. First, we did not compare the characteristics of those patients excluded in the screening process (identified as not having a high risk of stroke) with those included (identified as high risk of stroke) in our study because of a lack of data, so our results can only be applied to those at high risk of stroke. Second, this is a cross-sectional study, and further prospective studies should be conducted to better understand how much finding IPN adds to current stroke prediction tools.

CONCLUSIONS

TC, LDL-C, and non–HDL-C were positively associated with the presence of carotid IPN in a Chinese high–stroke-risk population.

ARTICLE INFORMATION

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Disclosures

None.

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