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Resistin might not be a risk factor for carotid artery atherosclerosis in elderly Chinese males

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Abstract

Objective To investigate the correlation between the serum resistin level and carotid artery atherosclerosis in elderly Chinese males. **Methods** The study enrolled 235 elderly Chinese males [median age 76 (range 60–97) years] scheduled for ultrasound examination of carotid artery plaque and determination of carotid artery intima-media thickness (CIMT). They were divided into carotid atherosclerotic plaque (CAP) and carotid atherosclerotic plaque-free (CAP-free) groups according to the ultrasound results. Their clinical profiles were collected, and the serum resistin and other blood biochemistry levels were determined. **Results** The CAP group was older and had a thicker mean CIMT than the CAP-free group. However, there was no difference in the serum resistin level between the groups. CIMT was positively correlated with age (r = 0.299, P < 0.001). The serum resistin level was not correlated with CIMT, even after controlling for age. Multiple linear regression analysis revealed that age (β = 0.001, P < 0.001) and body mass index (β = 0.002, P = 0.015) were significantly and positively correlated with the mean CIMT. Only age [odds ratio (OR): 1.159; 95% confidence interval (CI): 1.078–1.183, P < 0.001] was associated with the presence of carotid artery atherosclerotic plaque. The serum resistin level was not correlated with the mean CIMT or associated with the presence of carotid artery atherosclerotic plaque. **Conclusion** The results suggest that resistin might not be a risk factor for atherosclerosis in elderly Chinese males.

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Keywords: Resistin; Intima-media thickness; Atherosclerosis; The elderly

1 Introduction

In 2001, resistin, a member of a newly discovered family of cysteine secretory proteins called "resistin-like molecules" or "found in the inflammatory zone", was discovered during screening to identify potential targets of the insulin sensitizer in 3T3-L1 adipocytes.[1] Resistin is an adipose tissue-specific secreted protein in rodents, which is involved in hepatic glucose metabolism and might be a link between obesity and insulin resistance.[2,3] However, the human resistin gene and protein differ from their rodent counterparts,[4] and in humans, peripheral blood mononuclear cells are the main source of resistin.[5,6] Recombinant human resistin promotes human endothelial cell activation by up-regulating the expression of endothelin-1, adhesion molecules, and monocyte chemoattractant protein-1, as well as by impairing tumor necrosis factor receptor associated factor-3 function.[7–9] Resistin secreted from macrophages infiltrating atheromas affects endothelial function and stimulates vascular smooth muscle cell migration.[10] In population studies, resistin levels are correlated with coronary artery calcification in patients with a family history of premature coronary artery disease.[9] Plasma resistin levels are also correlated with previous heart disease in patients with end-stage renal disease.[11] Previously, our group found that serum resistin levels were correlated with triglycerides (TG), low-density-lipoprotein cholesterol (LDL-C), and C-reactive protein in 327 elderly Chinese males.[12]

These findings suggest a link between resistin and atherosclerosis via pro-inflammatory pathways. The carotid artery intima-media thickness (CIMT) is considered to be a marker of atherosclerosis.[13] The simplicity of assessing CIMT using B-mode ultrasound has great promise for the non-invasive determination of the presence of atherosclerosis.[14] However, it is still controversial whether resistin is involved in the progression of atherosclerosis. Shin, *et al*.[15]

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reported an independent association between the serum resistin level and increasing intima-media thickness (IMT) in treated hypertensive patients.

By contrast, Kunnari, *et al*.[16] did not find an independent association between resistin and early atherosclerosis. Therefore, this study assessed the cross-sectional relationship between resistin and carotid artery atherosclerosis in elderly Chinese males.

2 Methods

2.1 Study subjects

Between January 2011 and December 2012, a total of 235 consecutive elderly Chinese males [median age 81 (range 60–97) years] scheduled for ultrasound examination of the carotid arteries in the Chinese PLA General Hospital were recruited for this cross-sectional study. Our study was approved by the Ethics Committee of the Chinese PLA General Hospital and conducted under the principles of the Declaration of Helsinki. Informed consent was obtained from all patients before participation in this study.

The patients were divided into two groups according to the results of the ultrasound examination: the carotid atherosclerotic plaque (CAP, n = 173) and carotid atherosclerotic plaque-free (CAP-free, n = 62) groups. Carotid atherosclerotic plaque was defined as: (1) plaque encroaching into the arterial lumen by at least 0.5 mm or 50% of the surrounding IMT and (2) a thickness > 1.5 mm as measured from the media adventia interface to the intima lumen interface.[17]

Exclusion criteria include current smoker, recent febrile illness, inflammatory disease, active malignancy, concurrent use of steroids or other immunosuppressive agents, liver failure, acute myocardial infarction, and inability to give written informed consent.

2.2 Clinical examination

All patients were asked about their lifestyle and medical history and underwent a physical examination, a series laboratory tests, and body measurements. Blood samples were drawn from an antecubital vein after fasting for 8 h to TG, total cholesterol (TC), high-density-lipoprotein cholesterol (HDL-C), LDL-C, fasting blood glucose (FBG), and creatinine (Cr). Blood samples (9: 1 in 3.2% trisodium citrate, v: v) were centrifuged at 3000 r/min for 20 min; the supernatant was aliquoted and stored at –80°C. Serum resistin levels were measured using a human resistin ELISA kit (BioVender, German). Blood pressure (BP) was measured twice at 5-min intervals using a mercury sphygmomanometer. The Korotkoff first and fifth phase sounds were recorded as the systolic (SBP) and diastolic blood pressures (DBP), respectively. BP was defined as the average of two measurements. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Physicians' diagnoses of coronary heart disease (CHD), old myocardial infarction (OMI), congestive heart failure (CHF), hypertension, diabetes mellitus (DM), chronic kidney disease (CKD), peripheral arterial occlusive disease (PAOD), atrial fibrillation (AF), and current medication including statins and thiazolidinediones (TZDs) were collected. Patients who had taken statins for at least one year were recruited to our study.

2.3 Carotid ultrasonography

Ultrasonographic scanning of the carotid artery was performed by a single operator with an 8-MHz linear scanner (Sequoia C512; Acuson, Mountain View, CA). Patients were scanned in the supine position with the neck hyperextended. The CIMT was the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line, measured at the near and far walls of three 10 mm segments of the distal common carotid, bifurcation, and proximal internal carotid for both the left and right carotid arteries. For each of the 12 segments, the maximum IMT at the vessel wall free of atherosclerotic plaque was measured. The final CIMT was defined as the average of the maximum IMT at the 12 preselected sites. The mean CIMT was defined as the average CIMT of the right and left carotid arteries. The ultrasonographers were blinded to the levels of resistin levels.

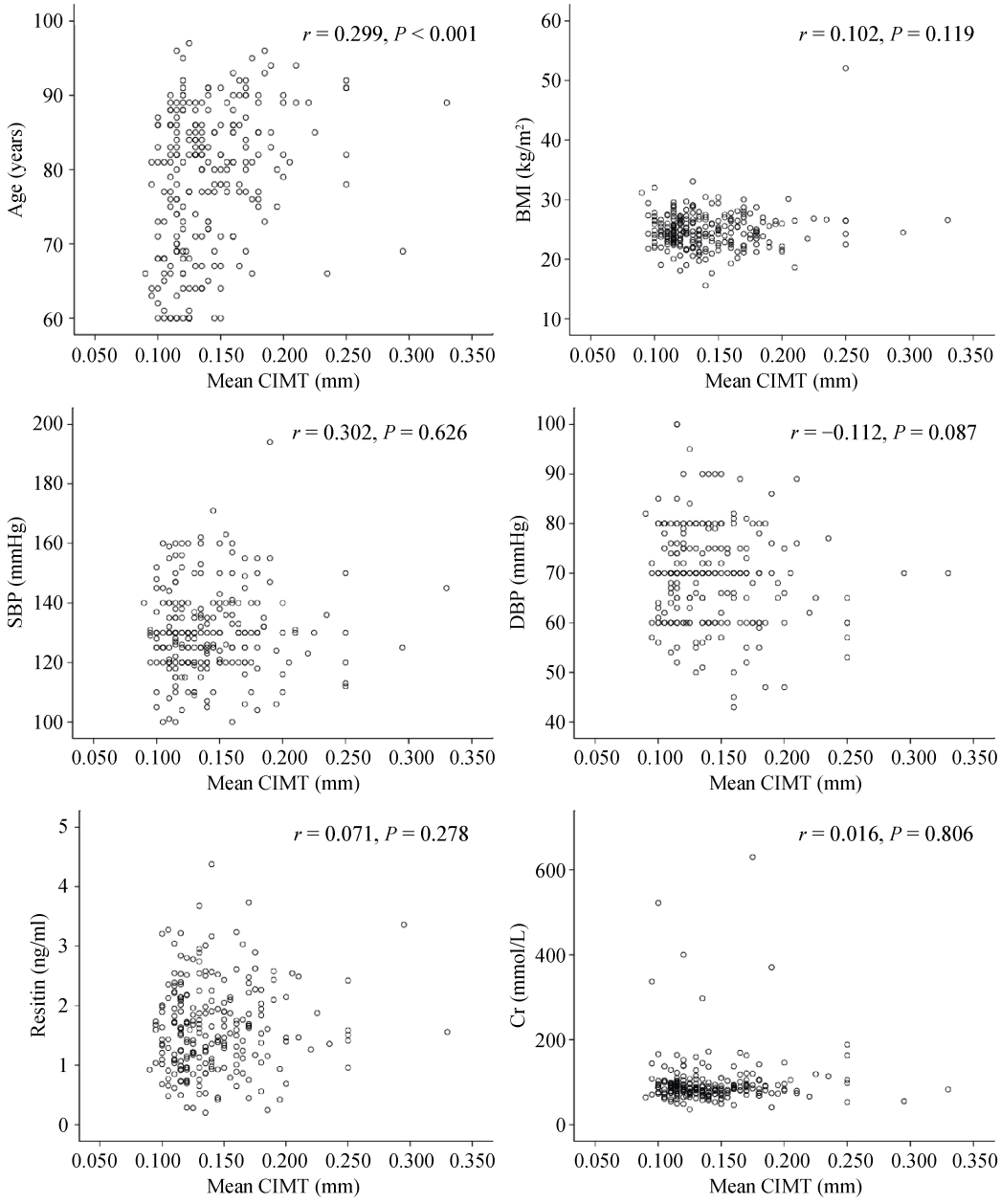
2.4 Statistical analysis

Based on the results of Liu's study,[18] the serum resistin level in the atherosclerosis group was 2.09 ± 1.12 ng/mL and the serum resistin level in control group was 1.43 ± 0.83 ng/mL. The difference of the mean resistin levels between the two groups was 0.63 (δ). The combined standard deviation (SD) of the two groups was 1.08 (σ). The probability of type Ⅰ error (α) was 0.05. The probability of type Ⅱ error (β) was 0.1. The sample size required in each group was 62 cases. Data were analyzed using SPSS 19.0 for Windows. Continuous variables were expressed as the mean ± SD. Categorical variables were expressed as percentages. Differences in continuous and categorical variables between groups were calculated using the independent samples *t*-test and chi-square test, respectively. Pearson's correlation and spearman's correlation of the mean CIMT with other continuous variables were determined. Partial correlation of the mean CIMT with other continuous variables was also tested controlling for age. Multiple linear regression analysis was

performed with the mean CIMT as the dependent variable, and by entering the independent variable with the highest correlation coefficient at each step, with an F-value probability for inclusion of 0.05 and 0.10 for removal. The effect of clinical parameters (i.e., age, BMI, BP, serum lipids profiles, FBG, creatinine (Cr), medical history, and medication) on the serum resistin level was also tested using multiple liner regression analysis. Binary logistic regression analysis was performed to determine potential predictors of carotid artery atherosclerotic plaque among clinical and laboratory variables. The odds ratio (OR) with the corresponding 95% confidence interval (CI) was calculated for each parameter. Entry was set at $P < 0.05$, with retention at $P < 0.10$. A receiver operating characteristic (ROC) curve was used for the predictive value of resistin for the presence of CAP. $P < 0.05$ was taken to indicate statistical significance.

3 Results

The clinical profiles of the study population are summarized in Table 1. Patients in the CAP group were, on average 10 years older, with a higher incidence of CHD and CKD morbidity, and a thicker mean CIMT than those in the CAP-free group. No differences in BMI, BP, serum lipid profiles, FBG, Cr, resistin, other medical history, or medication were found between the two groups.



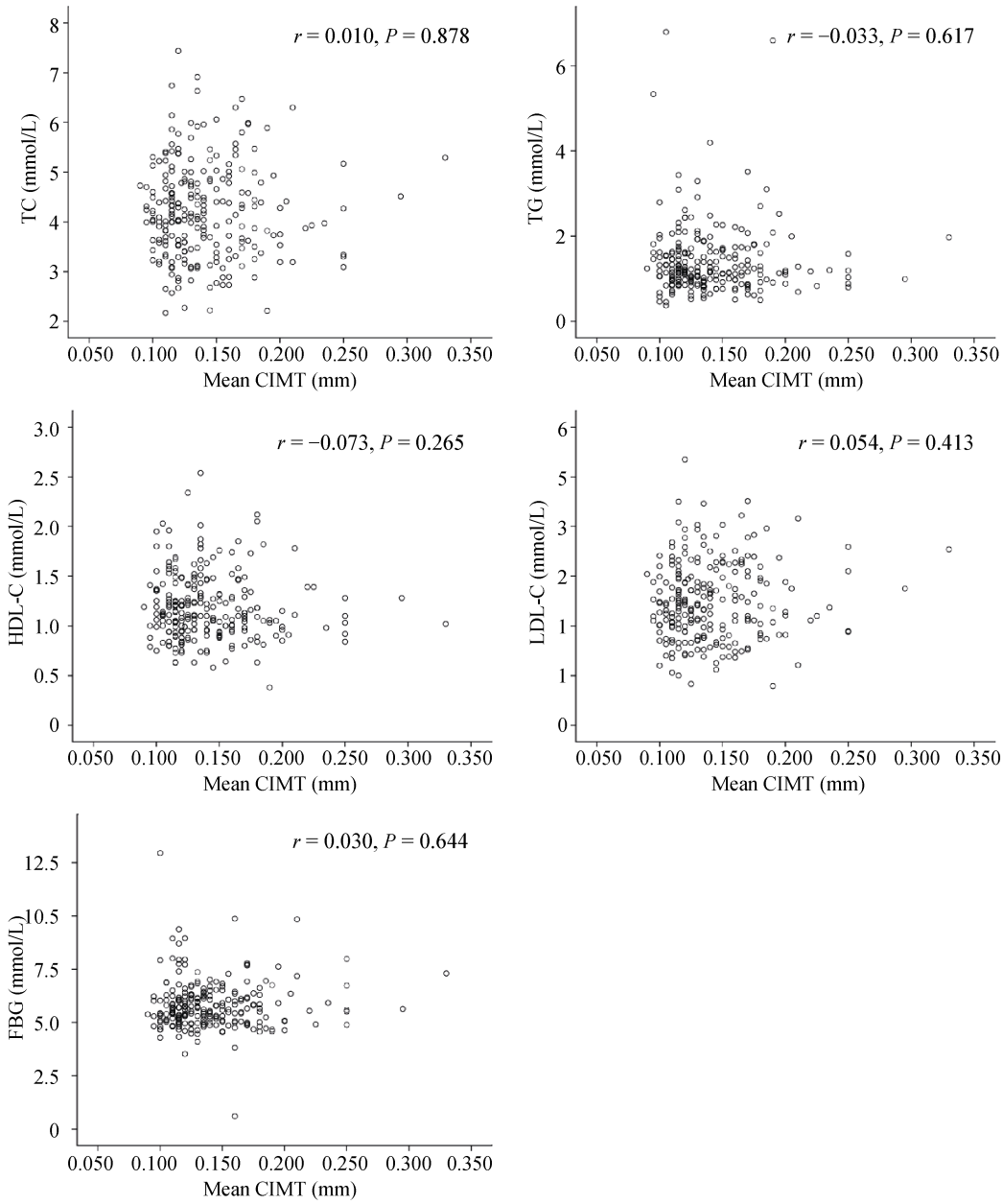


Figure 1. Spearman's correlations between the mean CIMT and age, BMI, SBP, DBP, Resistin, Cr, TC, TG, HDL-C, and LDL-C. ere investigated. Only age was positively correlated with the mean CIMT (r = 0.299, P < 0.001). BMI: body mass index; CIMT: carotid artery intima-media thickness; Cr: creatinine; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-C: high-density-lipoprotein cholesterol; LDL-C: low-density-lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides.

Bivariate correlations between the mean CIMT and the serum resistin level, age, BMI, BP, serum lipids profiles, FBG, and Cr were investigated are sown in Figure 1. A significant, positive correlation between the mean CIMT and age (r = 0.299, P < 0.001) was observed. The serum resistin level was correlated with age (r = 0.218, P = 0.001), Cr (r = 0.240, P < 0.001), and HDL-C (r = –0.158, P = 0.015). The correlation between the mean CIMT and serum resistin level was not significant (r = 0.071, P = 0.278). After controlling for age, a significant, positive correlation was found only between the mean CIMT and BMI (r = 0.159, P = 0.015). The serum resistin level was not correlated with CIMT (r = 0.006, P = 0.924), but was correlated with Cr (r = 0.204, P = 0.002) and HDL-C (r = –0.141, P = 0.03). Furthermore, correlations between the mean CIMT and the serum resistin level, age, BMI, BP, serum lipids profiles,

Table 1. Clinical profiles of the CAP and CAP-free groups.

	Overall cohort (*n* = 235)	CAP (*n* = 173)	CAP-free (*n* = 62)	*P*-value
Age, yrs	78.59 ± 9.68	81.25 ± 8.68	71.18 ± 8.44	<0.001
SBP, mmHg	130.29 ± 14.42	131.09 ± 15.15	127.97 ± 11.99	0.144
DBP, mmHg	69.49 ± 9.66	69.18 ± 9.77	70.26 ± 9.36	0.454
BMI, kg/m^2	24.80 ± 3.24	24.73 ± 3.50	24.99 ± 2.38	0.574
TC, mmol/L	4.22 ± 0.96	4.23 ± 1.00	4.21 ± 0.83	0.911
TG, mmol/L	1.41 ± 0.81	1.39 ± 0.74	1.45 ± 1.00	0.620
LDL-C, mmol/L	2.49 ± 0.78	2.51 ± 0.81	2.45 ± 0.71	0.611
HDL-C, mmol/L	1.19 ± 0.33	1.17 ± 0.35	1.24 ± 0.29	0.144
FBG, mmol/L	5.81 ± 1.16	5.79 ± 1.09	5.87 ± 1.34	0.678
Cr, mmol/L	98.11 ± 61.30	99.62 ± 63.90	93.91 ± 53.64	0.530
Mean CIMT, mm	1.41 ± 0.37	1.49 ± 0.35	1.16 ± 1.34	< 0.001
Resistin, ng/mL	1.63 ± 0.73	1.65 ± 0.75	1.55 ± 0.69	0.357
Medical history, *n* (%)				
CHD	137 (58.3%)	114 (65.9%)	23 (37.1%)	< 0.001
OMI	25 (10.6%)	22 (12.7%)	3 (4.8%)	0.084
Hypertension	154 (65.5%)	118 (68.2%)	36 (58.1%)	0.119
DM	110 (46.8%)	83 (48.0%)	27 (43.5%0	0.498
PAOD	69 (29.4%)	55 (31.8%)	14 (22.6%)	0.172
CKD	30 (12.8%)	27 (15.6%)	3 (4.8%)	0.029
CHF	19 (8.1%)	16 (9.2%)	3 (4.8%)	0.274
AF	29 (12.3%)	21 (12.2%)	8 (12.9%)	0.875
Concomitant therapy, *n* (%)				
Statin	143 (60.9%)	107 (61.8%)	36 (58.1%)	0.600
TZDs	11 (4.7%)	8 (4.6%)	3 (4.8%)	0.591

Data are presented as mean ± SD or *n* (%). AF: atrial fibrillation; BMI: body mass index; CAP: carotid atherosclerotic plaque; CHD: coronary heart disease; CHF: congestive heart failure; CIMT: carotid artery intima-media thickness; CKD: chronic kidney disease; Cr: creatinine; DBP: diastolic blood pressure; DM: diabetes mellitus; FBG: fasting blood glucose; HDL-C: high-density-lipoprotein cholesterol; LDL-C: low-density-lipoprotein cholesterol; OMI: old myocardial infarction; PAOD: peripheral arterial occlusive; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; TZDs: thiazolidinediones.

FBG, and Cr were determined by spearman correlation. The mean CIMT was only correlated with age (r = 0.212, P < 0.001). The correlation between the mean CIMT and serum resistin level was also not significant (r = 0.066, P = 0.312).

Multiple linear regression analysis was used to assess the effect of clinical parameters (i.e., age, resistin, BMI, BP, serum lipids profiles, FBG, Cr, medical history, and medication) on the mean CIMT. Only age (β = 0.001, P < 0.001) and BMI (β = 0.002, P = 0.015) were significant in all subjects. The equation was calculated as the mean CIMT = 0.002 + 0.001 × age + 0.002 × BMI.

Furthermore, only age (OR: 1.159; 95% CI: 1.078–1.183, P < 0.001) was associated with the presence of carotid artery atherosclerotic plaque in the binary logistic regression analysis. The serum resistin level was not associated with the presence of carotid artery atherosclerotic plaque (Table 2). The ROC curve showed that an area under the ROC curve for resistin predicted the presence of carotid artery atherosclerotic plaque was 0.536 (P = 0.406; 95%CI: 0451–0.620).

The effects of clinical parameters (i.e., age, BMI, BP, serum lipids profiles, FBG, Cr, medical history, and medication) on the serum resistin level were further assessed using multiple liner regression analysis. This showed that age (β = 0.012, P = 0.011), Cr (β = 0.002, P = 0.002), and HDL-C (β = –0.294, P = 0.034) were significant in all subjects. The equation was mean serum resistin level = 0.761 + 0.002 × Cr + 0.012 × age – 0.294 × HDL-C.

Table 2. Binary logistic regression: risk factors for the presence of CAP.

	OR	95% CI	*P*-value
Age	1.129	1.078–1.183	< 0.001
BMI	0.996	0.893–1.111	0.950
SBP	1.001	0.972–1.032	0.924
DBP	1.027	0.984–1.071	0.225
TC	2.909	0.494–17.124	0.238
TG	0.500	0.235–1.065	0.072
HDL-C	0.133	0.017–1.060	0.057
LDL-C	0.461	0.072–2.952	0.414
Resistin	0.843	0.503–1.412	0.516
Statins	1.241	0.575–2.677	0.582
TZDs	1.664	0.322–8.591	0.543
CHD	0.523	0.233–1.177	0.117
Hypertension	0.920	0.432–1.959	0.829
DM	0.916	0.427–1.965	0.822
PAOD	0.886	0.369–2.130	0.788
CKD	0.305	0.046–2.020	0.218

BMI: body mass index; CAP: carotid atherosclerotic plaque; CHD: coronary heart disease; CHF: congestive heart failure; CIMT: carotid artery intima-media thickness; CKD: chronic kidney disease; Cr: creatinine; DBP: diastolic blood pressure; DM: diabetes mellitus; FBG: fasting blood glucose; HDL-C: high-density-lipoprotein cholesterol; LDL-C: low-density-lipoprotein cholesterol; PAOD: peripheral arterial occlusive; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; TZDs: thiazolidinediones.

4 Discussion

In this cross-sectional study, age was positively correlated with the mean CIMT (β = 0.259, P = 0.002) and considered a risk factor for carotid artery atherosclerotic plaque (OR: 1.159; 95% CI: 1.078–1.183, P < 0.001). Obviously, there was a 10-year difference in age between the two groups. The mean CIMT in the CAP group was 0.33 mm thicker than in the CAP-free group, which could be attributed to a mean change in the CIMT of 0.0147 mm/year based on the results of 13 studies.[19] Even after controlling for age, a significant, positive correlation was found only between the mean CIMT and BMI (r = 0.159, P = 0.015). We did not find a significant correlation between the serum resistin level and mean CIMT or show that the serum resistin level was a risk factor for carotid artery atherosclerotic plaque, which reflects the body-wide progression of arterial atherosclerosis. Our results are consistent with those of Kunnari,[16] who did not demonstrate an independent association between resistin and early atherosclerosis defined by IMT. However, our results are not consistent with the finding that the plasma resistin level was positively associated with coronary artery calcification.[20]

This discrepancy could be attributed to the difference in subject selection. In our study, the subjects were elderly Chinese males (median age 81) with a positive medical history. The respective percentages of subjects diagnosed with CHD, MI, hypertension, DM, PAOD, RD, HF, and AF were 58.3%, 10.6%, 65.5%, 46.8%, 29.4%, 12.8%, 8.1%, and 12.3%, respectively. In Reily's study, the subjects were healthy males 30–65 years old (median age 46), or females 35–70 years old (median age 50) who had only a family history of premature CAD, while all subjects with evidence of clinical CAD were excluded.[20] They examined a younger healthy population with relatively low cardiovascular risk, whereas we examined a much older population with relatively high risk. Second, the discrepancy could be explained by the different methods used to measure atherosclerosis. They used coronary artery calcification to quantify coronary atherosclerosis, as coronary artery calcification was found to predict cardiovascular diseases events in asymptomatic samples.[20] By contrast, we used CIMT to quantify atherosclerosis, which is not only a marker of early atherosclerosis, but also an independent marker of future cardiovascular events, such as MI and stroke.[21] Third, the influence of statins on the resistin level must also be considered. Another study reported that 12 weeks of statin therapy significantly decreased the resistin levels in 42 patients (mean age 62.5 ± 12.6 years) from 17.1 ± 9.9 ng/dL to 15.2 ± 10.0 ng/dL.[22] The specific mechanism is still unclear, but it is suggested that statins have a reductive effect on preventing the release of resistin from macrophages, as well as anti-inflammatory and anti-atherosclerotic pleiotropic effects.[23] In our study, the percentage of patients on statins was 61.8% in the CAP group and 58.1% in the CAP-free group. In comparison, 17.8% of the males and 10.4% of the females in Reily's study were on statin therapy. Obviously, the duration of statin therapy (at least one year) in our study exceeded 12 weeks. The long-term use of statins in 60.9% of our subjects would inevitably reduce the resistin levels and improve the serum lipid profiles in our study population, which might lead to a reduction of the significance of resistin in atherogenesis.

Furthermore, in our study, the serum resistin level was significantly correlated with Cr (r = 0.240, P < 0.001), and this significance remained after controlling for age (r = 0.204, P = 0.002). A recent study of 30 patients indicated that the glomerular filtration rate was the only independent predictor of plasma resistin level.[24] The serum resistin level might be correlated with renal function.

There were several limitations in our study. First, the results of our study might be underpowered because of the cross-sectional design based on a single medical centre and the relatively small sample size. Second, the source of resistin in our study was not investigated. Previous studies have demonstrated that increasing resistin levels indicate increased monocyte activity, as resistin is strongly expressed in monocytes.[25] Since monocytes play an important role in atherogenesis, resistin might be indirectly involved in the development of atherosclerosis. But the causality could not be made by the results of our study. Third, the subjects of the control group (CAP-free group) were not healthy subjects, which might interfere with the results of our study. The essential role of resistin in atherosclerosis needs further investigation in animal models and large-scale human studies.

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