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ORIGINAL ARTICLE

The association of serum chemerin level with risk of coronary artery disease in Chinese adults

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Abstract Chemerin is a newly discovered adipokine which has been found closely associated with obesity, metabolic syndrome (MetS), and inflammatory status. This study will investigate whether serum chemerin levels are associated with coronary artery disease (CAD) independently of other cardiovascular risk factors. This study included a total of 430 subjects (239 with CAD and 191 with non-CAD) who underwent coronary angiography. Anthropometric measurements were performed and chemerin, glucose, lipid profiles, and other biochemical characteristics were measured. The severity of coronary atherosclerosis was estimated by the total number of diseased vessels and Gensini score. Serum chemerin levels were significantly higher in the CAD group than in the non-CAD group ($P = 0.011$). The odds ratios (95% CI) of CAD across increasing quartiles of serum chemerin were 1.04 (0.61–1.78), 1.08 (0.63–1.83), and 1.87 (1.07–3.24), ($P = 0.386$, 0.508, and 0.012, respectively). Adjusting for age, sex, and other conventional risk factors for CAD did not appreciably alter the results. Serum chemerin levels were significantly increased with an increasing of number of diseased vessels ($P = 0.024$). In conditional linear regression models, chemerin levels were positively related to Gensini score even after established cardiovascular risk factors ($\beta = 0.13$, $P = 0.019$). Correlation analysis showed serum chemerin levels were significantly associated with TG levels, TC levels, fasting serum insulin, HOMA-IR and MetS (all $P < 0.05$). Higher serum chemerin levels were associated with increased risk of CAD and metabolic parameters in Chinese adults. Chemerin may represent a novel link between metabolic signals and atherosclerosis.

Keywords Chemerin · Coronary artery disease · Coronary angiography · Insulin resistance

Abbreviations

CAD	Coronary artery disease
HOMA-IR	Homeostasis model assessment index of insulin resistance
OR	Odds ratio
CI	Confidence interval
BMI	Body mass index
TG	Triglyceride
TC	Total cholesterol
HDL-c	High density lipoprotein cholesterol
LDL-c	Low density lipoprotein cholesterol
MetS	Metabolic syndrome

Introduction

Adipokines have important roles in the regulation of systemic lipids and glucose metabolism through systemic actions in the brain, liver, and muscle. Adipokine secretion and blood levels are mostly affected by the degree of

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adiposity, leading to the hypothesis that dysregulation of pro-inflammatory and anti-inflammatory adipokines secretion in obesity may serve as a pathogenic link between obesity, metabolic syndrome (MetS), and cardiovascular diseases [1–5].

Chemerin is a newly discovered adipokine which modulates chemotaxis and activation of dendritic cells and macrophages, as well as modulates adipocyte differentiation through distinct G protein-coupled receptors such as CMKLR1, GPR1, and CCRL2 [2, 6–11]. Recently, several studies have reported that circulating chemerin levels were associated with not only markers of inflammation [12–14] but also components of MetS including body mass index (BMI), triglycerides, HDL cholesterol and hypertension [6, 14, 15]. However, its relationship with insulin resistance and type 2 diabetes is controversial [6, 15]. Furthermore, the correlation of chemerin and atherosclerosis has also been suspected, and two recent studies in humans evaluated the association of chemerin with coronary atherosclerosis in different aspects [14, 16]. Spiroglou et al. demonstrated the positive correlation of atherosclerosis and local chemerin expression in both human periaortic and pericoronary adipose tissue depots [16]; Lehrke et al. [14] found a weak association of systemic chemerin levels with coronary plaque burden and the non-calcified plaque using CT-angiography in Caucasian subjects. However, the associations were lost after adjusting for established cardiovascular risk factors. Therefore, the definitive association of systemic chemerin levels with coronary atherosclerosis remains uncertain and it is necessary to further establish these relationships using different methods in different populations.

The aim of this study is to examine whether serum levels of chemerin are associated with metabolic parameters and the severity of coronary atherosclerosis in the subjects who had undergone coronary angiography for the diagnosis of coronary artery disease (CAD), and to evaluate the role of chemerin levels as a potential novel cardiovascular risk factor.

Subjects and methods

Study participants

For inclusion in this study, we considered 493 consecutive patients who were referred to the department of cardiology in Ruijin Hospital (Shanghai) due to the symptoms in the chest such as chest pain, chest heaviness, periodic discomfort, and palpitations in the period from January 2005 to December 2007. Those with medical illnesses such as acute infection, chronic hepatic and renal dysfunction (including serum alanine aminotransferase >120 IU/l, and aspartate aminotransaminase >80 IU/l, and serum creatinine >2.0 mg/dl), or nutritional derangements, malignancies and other severe medical illnesses were excluded ($n = 63$). Thus, the present analysis included 430 (279 men and 151 women, age range 39–84 and 45–85; mean 61.7 and 62.8, respectively) patients. All subjects were Chinese living in the Shanghai region and gave informed consent. This study was approved by the Institutional Review Board of the Ruijin Hospital, and complied with the Declaration of Helsinki.

Clinical and biochemical measurements

All subjects were screened with regard to medical history (i.e., date of birth, smoking, alcohol consumption, and medical treatments). Height and weight (with light-weight clothing and without shoes), waist and hip circumferences and seated blood pressure were determined by the same observer. BMI was calculated as weight (kg) divided by the square of height (m).

The 75-g oral glucose tolerance test was performed in all subjects between 0700 and 0800 h following overnight fasting and before coronary angiography. Venous blood samples were collected during fasting and at 2 h after glucose loading for the measurement of fasting plasma glucose, fasting serum insulin, hemoglobin A1c (HbA1c), triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), 2 h plasma glucose, and 2 h serum insulin. The blood samples were frozen at −80°C until assayed. Plasma glucose level was measured immediately after blood centrifugation using an enzymatic method (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA). Fasting insulin and 2 h insulin levels were measured using a double antibody radioimmunoassay by enzymatic methods (DSL, Webster, Texas, USA). Fasting serum levels of triglycerides and total cholesterol were measured by enzymatic methods (Beckman coulter Inc, Fullerton, CA, USA). High density lipoprotein cholesterol and low density lipoprotein cholesterol were measured by enzymatic methods (HDL-c, LDL-c Direct, Wake Pure Chemical Industries Ltd. GmbH, Neuss, Germany). Glycated hemoglobin was measured by high performance liquid chromatography using the BioRad Variant HbA1c assay (Hercules, CA, USA). Serum chemerin was measured and homeostasis model assessment index (HOMA-IR) was calculated using the following formula: [FINS (μIU/ml) × FPG (mmol/l)]/22.5 [17].

Serum chemerin levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R & D Systems, USA), according to the manufacturer's protocol, with the intra-assay and inter-

assay CVs for pooled human serum of 9 and 11%, respectively.

Coronary angiography and diagnostic criteria for CAD

Coronary angiography was performed in multiple projections with the Judkins technique. Coronary stenosis with lumen narrowing ≥50% were considered significant. CAD was diagnosed as the presence of one or more vessels with significant stenosis in a given subject. The severity of coronary atherosclerosis was defined as the number of diseased vessels by a ranked variable with significant stenosis in a given subject and the Gensini score as a continuous variable which was based on the number of stenotic coronary artery segments and the degree of lumen stenosis [18].

Definitions of MetS

In the present analysis, we used the updated 2005 National Cholesterol Education Program Adult Treatment Panel III criteria to define MetS [19]. In details, the definition of MetS requires the presence of any 3 or more of the following 5 criteria: (1) high blood pressure: blood pressure ≥130/85 mmHg or known treatment for hypertension, (2) hypertriglyceridemia; fasting plasma triglycerides ≥1.7 mmol/l, (3) low HDL: fasting HDL cholesterol <1.0 mmol/l in men, <1.3 mmol/l in women; (4) hyperglycemia: fasting glucose level of ≥6.1 mmol/l or known treatment for diabetes, (5) central obesity: waist circumference >90 cm in men, >80 cm in women.

Statistical analysis

Unless denoted otherwise, categorical data are described as percentages and continuous data are described as means ± SD or median (inter-quartile range). Logarithmic transformation was used for serum insulin, HOMA-IR, chemerin and Gensini score due to the high degree of skewing. A student's t test (for data that was normally distributed) or a Mann–Whitney test (for data that was not normally distributed) and χ^2 test (for data that were categorical variables) were used to compare the CAD and non-CAD samples. Correlations between serum chemerin levels and continuous variables were determined using Pearson's correlation (for normally distributed data) or Spearman's correlation (for non-normally distributed data).

Odds ratios (ORs) of CAD were calculated using logistic regression models, adjusting for covariates including age, sex, BMI, smoking, alcohol, family history of CAD, and additional biochemical risk factors of LDL-c, HDL-c, TG, and diabetes. Serum chemerin levels were analyzed in quartiles with the lowest quartile (Q1) as the reference. Multivariable linear regression modeling was used to examine serum chemerin levels as a factor associated with number of diseased vessels and Gensini score. P values <0.05 were considered significant. All analyses were performed using software package SPSS 13.0 for Windows® (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Clinical characteristics of subjects in CAD ($N = 239$) and non-CAD ($N = 191$) groups were summarized in Table 1. Because the study design allowed for a variable number of controls for each case, it was not unexpected that cases were more often male, were more likely to smoke and drink alcohol, be diabetic, and have higher insulin resistance levels and blood pressure levels compared with controls. As expected, the MetS rate in CAD group was significantly higher than that in non-CAD group (59.6 vs. 42.1%, $P < 0.01$). There were no significant differences between the CAD and non-CAD groups with respect to age, BMI, waist circumference, and lipid profiles.

Association of serum chemerin with anthropological and metabolic variables

Logarithmic transformation of chemerin (Lgchemerin) was significantly associated with TG, TC, fasting serum insulin and Logarithmic transformation of HOMA-IR (lgHOMA-IR) ($r = 0.11$, $P = 0.023$; $r = 0.11$, $P = 0.033$; $r = 0.19$, $P = 0.001$; and $r = 0.20$, $P = 0.001$, respectively), and was marginally associated with diastolic blood pressure and LDL-c ($r = 0.09$, $P = 0.055$; $r = 0.093$, P = 0.054, respectively). The association of chemerin levels with age, BMI, waist circumference, and glucose levels in these samples (all $P > 0.05$) was not identified.

We also explored the associations of serum chemerin with MetS. The median concentration of chemerin in the serum of MetS group ($n = 227$) was 49.1 (38.7, 58.3) ng/ml, significantly higher than that of the non-MetS group ($n = 203$), which was 44.7 (36.5, 54.9) ng/ml ($P = 0.040$) (Fig. 1a). When all the subjects were further divided into four groups according to the CAD and MetS status (non-CAD/non-MetS, non-CAD/MetS, CAD/non-MetS, and CAD/MetS groups), no difference was found in serum chemerin levels in non-CAD and CAD groups according to the MetS status (different $P > 0.05$) (Fig. 1b).

Table 1 Clinical characteristics of subjects in CAD and non-CAD groups

	CAD	Non-CAD	*P* value*
No. (male/female)	239 (184/55)	191 (96/95)	<0.001
Age, year	62.5 ± 8.5	61.7 ± 8.9	0.326
BMI, kg/m^2	25.2 ± 3.4	25.5 ± 3.2	0.352
Waist circumference, cm	90.3 ± 8.9	91.0 ± 7.8	0.436
SBP, mmHg	133 ± 19	127 ± 18	0.025
DBP, mmHg	80 ± 10	78 ± 11	0.149
Current smokers, *n* (%)	117 (49.0)	49 (27.1)	<0.001
Alcohol use, *n* (%)	47 (19.7)	18 (9.4)	0.004
History of type 2 diabetes, *n* (%)	81 (33.9)	47 (24.6)	0.037
History of hypertension, *n* (%)	170 (71.1)	121 (66.9)	0.097
Family history of CAD, *n* (%)	46 (19.2)	27 (14.1)	0.196
TG, mmol/l	1.94 ± 1.06	1.93 ± 1.22	0.906
Total cholesterol, mmol/l	4.57 ± 1.07	4.59 ± 1.00	0.818
HDL-c, mmol/l	1.17 ± 0.34	1.21 ± 0.31	0.235
LDL-c, mmol/l	2.73 ± 0.99	2.70 ± 0.77	0.752
Fasting plasma glucose, mmol/l	5.7 ± 1.9	5.5 ± 1.5	0.035
2-h plasma glucose, mmol/l	9.3 ± 3.9	8.6 ± 3.6	0.057
HbA1C, %	6.7 ± 1.4	6.3 ± 1.1	0.006
Fasting serum insulin, μIU/ml	10 (4.9, 15.3)	7.8 (5.0, 11.4)	0.087
2-h serum insulin, μIU/ml	51.2 (26.6, 112.5)	44.8 (25.2, 98.9)	0.151
HOMA-IR, μIU mol/l^2	2.31 (1.22, 4.00)	1.64 (1.16, 2.50)	0.042
MetS, *n* (%)	143 (59.6)	80 (42.1)	<0.001

CAD Coronary artery disease, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TG* triglyceride, *LDL-c* low density lipoprotein cholesterol, *HDL-c* high density lipoprotein cholesterol, *MetS* metabolic syndrome

**P* values <0.05 were considered significant

Serum chemerin and CAD

The median concentration of chemerin in the serum of CAD group was 48.7 (38.9, 58.7) ng/ml, significantly higher than that of the non-CAD group, which was 45.7 (37.1, 56.7) ng/ml ($P = 0.011$) (Fig. 2). Serum chemerin was similar in females and males indicating that there is no gender dimorphism in these subjects.

Table 2 shows the associations between serum chemerin level (in quartiles) and CAD risk. In the crude analysis (Model 1), the ORs (95% CI) of CAD across increasing quartiles of serum chemerin were 1.04 (0.61–1.78), 1.08 (0.63–1.83), and 1.87 (1.07–3.24) ($P = 0.386$, 0.508, and 0.012, respectively). Also performed were a series of analyses in Model: (2), sex, and age; (3) age, sex, BMI, smoking, alcohol, and family history of CAD; and (4) age, sex, BMI, smoking, alcohol, family history of CAD, SBP, DBP, LDL-c, HDL-c, TG, and diabetes. The adjustment for the covariates did not appreciably change the associations.

Chemerin and the severity of coronary atherosclerosis

When all subjects were further divided into four groups according to the number of diseased vessels ($n = 0$, 1, 2, ≥ 3), the serum chemerin levels were 44.8 (36.4, 53.8), 47.2 (39.1, 57.6), 49.1 (41.1, 59.8), and 50.3 (42.1, 59.7) ng/ml for the subjects with diseased vessels of 0, 1, 2, and ≥ 3, respectively ($P = 0.024$). The levels of chemerin in the subjects with none diseased vessel were significantly lower than those with diseased vessels of 1, 2, and ≥ 3 ($P = 0.030$, $P = 0.025$, $P = 0.028$, respectively). The serum chemerin levels were not significantly different among groups with diseased vessels ≥ 1 (Fig. 3).

Table 3 represents the results for the series of linear regression models by association of lgchemerin with Gensini score for the previous 3 models in all subjects. Serum chemerin levels were associated with Gensini scores even after adjustment for age, sex, and other established risk factors of CAD ($\beta = 0.13$, $P = 0.019$).

Discussion

In this study, the relationship of circulating chemerin with the presence of CAD, the severity of coronary atherosclerosis, as well as metabolic variables in a cohort of subjects who had undergone coronary angiography were examined. It was determined that serum chemerin levels were

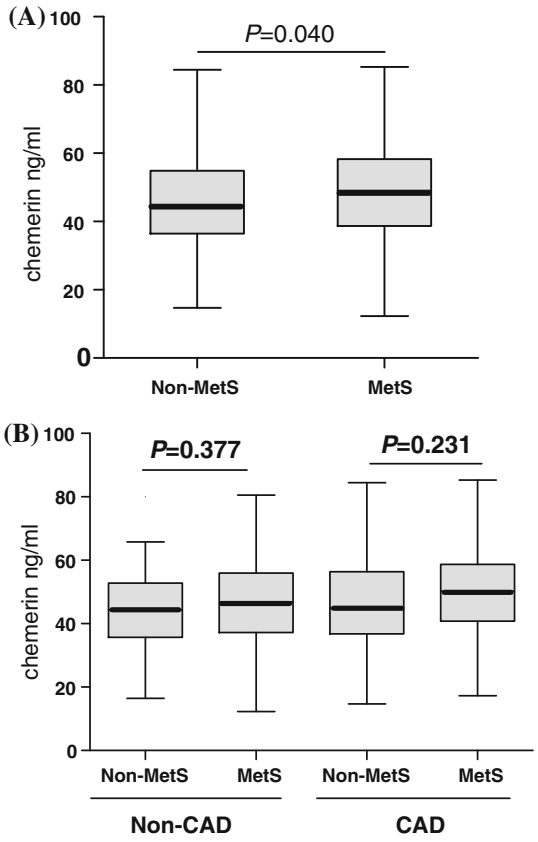

Fig. 1 The comparison of serum chemerin between MetS and non-MetS groups in the whole subjects (**a**) or according to the MetS status (**b**). *MetS* metabolic syndrome

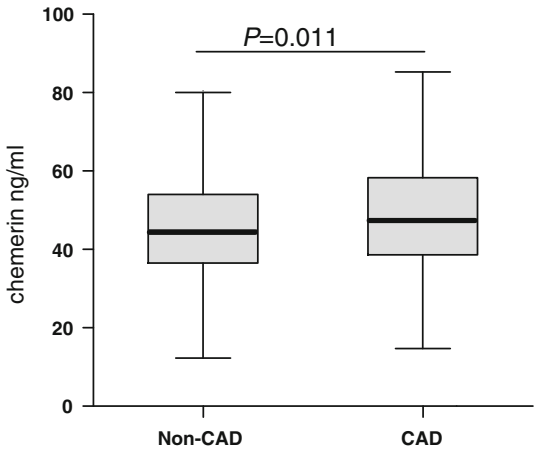

Fig. 2 The comparison of serum chemerin between CAD and non-CAD groups. *CAD* coronary artery disease

associated with TG levels, TC levels, serum insulin levels, HOMA-IR, and MetS. Furthermore, it was determined that serum chemerin levels were significantly higher in the CAD group than the non-CAD group, and was independently associated with odds of CAD and severity of coronary atherosclerosis after adjustment for established risk factors.

Recently, the associations of serum chemerin and coronary atherosclerosis were investigated in several studies [14, 20]. Lehrke et al. [14] found that chemerin levels were weakly correlated with coronary plaque burden and the number of non-calcified plaques in subjects undergoing CT-angiography. Hah et al. further investigated the relationship of serum chemerin with cardiometabolic parameters in Korean patients with CAD. They found that serum chemerin levels correlated positively with the degree of coronary artery stenosis and fasting glucose, triglyceride, total cholesterol, low density lipoprotein cholesterol, and high sensitive C-reactive protein levels. Multiple binary logistic regressions showed chemerin was not an independent risk factor of multiple vessel disease. However, serum chemerin levels were not compared in subjects with and without CAD in this study [20]. In this study, we examined the serum chemerin levels in subjects who underwent coronary angiography and found that serum chemerin levels were positively correlated with the risk of CAD and the severity of coronary atherosclerosis. Furthermore, we found that adjustments of other traditional risk factors do not appreciably change these associations, which might be different from the previous studies.

Cholesterol uptake and efflux experiments demonstrated that there was a significant increase in total cholesterol in human monocyte-derived macrophages treated with chemerin. Rosiglitazone can cause an increase in cholesterol efflux from monocytes with a corresponding decrease in the expression of CMKLR1 [21]. Spiroglou et al. found a positive correlation between atherosclerosis and chemerin expression in both periaortic and pericoronary adipose tissue depots, as well as between aortic atherosclerosis and aortic VSMC and foam cell chemerin expression [16]. Chemerin was found highly expressed in white fat tissue, regulating adipogenesis and adipocyte metabolism [1, 2], as well as inducing insulin resistance in primary human skeletal muscle cells [22]. Functional angiogenesis assays in human endothelial cells confirmed that chemerin-induced endothelial angiogenesis [23, 24]. Insulin resistance is associated with hyperinsulinemia, obesity, hypertension, and abnormalities of several nontraditional risk factors such as endothelial dysfunction and inflammation [25, 26]. Even in the absence of other traditional cardiovascular risk factors, insulin resistance is associated with endothelial dysfunction in the peripheral and coronary arteries [27]. Growing evidence supports a potential role for cytokine-associated, subacute inflammation in the pathogenesis of insulin resistance and atherosclerosis [28–30]. In this study, we found that serum chemerin was related to fasting insulin levels and HOMA-IR. These data, combined with the current results, suggest chemerin might

Table 2 Associations between serum chemerin (in quartiles) and the risk of CAD

	OR (95% CI)			
	Q1	Q2	Q3	Q4
Serum chemerin level, median (range), ng/ml	30.8 (24.2–34.0) ($n = 90$)	41.0 (38.5–42.8) ($n = 103$)	49.7 (47.1–52.1) ($n = 100$)	62.0 (57.8–67.1) ($n = 137$)
Model 1: crude: no adjustment	1.0	1.04 (0.61, 1.78)	1.08 (0.63, 1.83)	1.87 (1.07, 3.24)
P values		0.386	0.508	0.012
Model 2: adjusting for age, sex	1.0	0.98 (0.56,1.72)	1.09 (0.62,1.90)	1.98 (1.11,3.53)
P values		0.241	0.563	0.007
Model 3: adjusting for age, sex, BMI, smoking, alcohol, and family history of CAD	1.0	0.96 (0.53, 1.73)	1.03 (0.57, 1.85)	1.88 (1.05, 3.46)
P values		0.289	0.498	0.015
Model 4: adjusting for age, sex, BMI, smoking, alcohol, family history of CAD, SBP, DBP, LDL-c, HDL-c, TG, and diabetes	1.0	0.84 (0.45, 1.57)	1.06 (0.57, 1.99)	1.99 (1.04, 3.79)
P values		0.105	0.672	0.007

Q1–4 Quartile 1–4

Odds ratios (ORs) of CAD were calculated using logistic regression models. Serum chemerin level was analyzed in quartiles with the lowest quartile (Q1) as the reference. Abbreviations see Table 1

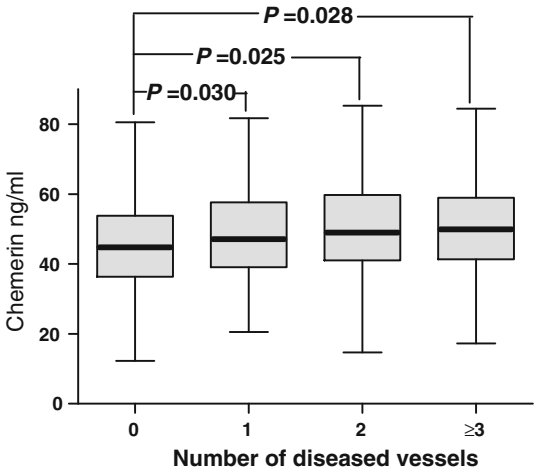

Fig. 3 The comparison of serum chemerin according to the number of stenotic coronary arteries

play a role in macrophage cholesterol uptake and foam cell formation, as well as be a potential link between insulin resistance and endothelial dysfunction, like IL-6 and adiponectin [28, 29].

In our study, it was also determined that serum chemerin was related with serum TG and TC levels; furthermore, it was associated with MetS. However, we failed to find the association between chemerin with age, BMI, and waist circumference which might be partly due to the ethnic diversity. These results could be confirmed by another Asian population study [20].

Some limitations of the study merit discussion. First, the study subjects might be heterogeneous in treatments for diabetes and cardiovascular disease, thus all influences of drugs could not be eliminated. However, adjustment of the medication use did not change the major findings. Second, this study was cross-sectional in nature and the sample size was relatively small. Therefore, it led to the lack of significance for usual CAD risk factors and no claim regarding causality could be made and would be cautious in interpretations of the findings.

In conclusion, in this study it was determined that high chemerin levels were associated with increasing risk of CAD and severity of atherosclerosis independently of other cardiovascular risk factors. In addition, serum chemerin

Table 3 Multivariable association of serum chemerin levels with Gensini score

Adjusted for	β	*P*
Model 1: adjusting for age, sex	0.13	0.009
Model 2: adjusting for age, sex, BMI, smoking, alcohol, and family history of CAD	0.14	0.006
Model 3: adjusting for age, sex, BMI, smoking, alcohol, family history of CAD, SBP, DBP, LDL-c, HDL-c, TG, and diabetes	0.13	0.019

Abbreviations see Table 1

levels were also associated with lipid profile, insulin resistance, and MetS. These results indicated that chemerin might present a novel link between metabolic signals and atherosclerosis. Further studies are awaited to confirm our current findings and explore whether chemerin could be a marker in the prediction of overt or silent CAD [31, 32] in these patients.

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Conflicts of interest The authors declared that they have no conflicts of interests.

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