Chemerin is not associated with subclinical atherosclerosis markers in prediabetes and diabetes

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Abstract

Objective: Chemerin is a novel adipokine that is correlated with adipocyte differentiation, glucose metabolism, and inflammation. We aimed to investigate the relation between serum chemerin level and subclinical atherosclerosis markers as exemplified by brachial artery pulse wave velocity (baPWV), carotid intima–media thickness (CIMT), epicardial fat thickness (EFT), and carotid plaque presence in diabetes and prediabetes.
Methods: Age-, body mass index (BMI)-, and gender-matched patients with type 2 DM (n=30), prediabetes (n=25), and normal glucose tolerance (n=25) were included in this cross-sectional study. Serum chemerin level, lipid parameters, glucose metabolism marker, baPWV, CIMT, EFT, and anthropometric were recorded. The independent risk factors for atherosclerosis markers were determined by linear and/or multiple logistic regression analysis.
Results: baPWV and carotid plaque presence were higher in the diabetes group than in prediabetes and control groups (p=0.039 and p=0.035 respectively), whereas serum chemerin levels were similar among groups (p=0.338). Chemerin levels were not correlated with PWV, CIMT, and epicardial fat thickness overall or in the subgroups. Overall and in the diabetes group, chemerin levels were positively correlated with the key components of metabolic syndrome as BMI, total body fat percentage, waist circumference, triglyceride, and systolic and diastolic blood pressure (BP). After adjusting for age, gender, and BMI, only the association between chemerin and systolic BP remained significant. Chemerin was not found as an independent risk factor for predicting atherosclerosis in diabetes and prediabetes.
Conclusion: Chemerin is not a predictive marker for atherosclerosis in diabetes and prediabetes, but correlates well with key aspects of the metabolic syndrome particularly in diabetes. *(Anatol J Cardiol 2016; 16: 749-55)*
Keywords: chemerin, diabetes, pulse wave velocity, atherosclerosis, carotid plaque, epicardial fat

Introduction

Diabetes is a major risk factor for cardiovascular diseases; however, the underlying mechanisms that link type 2 diabetes with cardiovascular disease remains elusive. Recent evidence suggests that adipokines integrating metabolic and inflammatory signals are attractive for assessing risk of atherosclerotic cardiovascular disease (1).

Chemerin is a recently identified novel adipokine that regulates adipocyte development and metabolic functions as well as adaptive and innate immunity (2–4). The inflammogen tumor necrosis factor-α stimulates chemerin production from adipocytes, thereby linking chemerin to inflammation (5). Chemerin promotes the recruitment of immature dendrite cells and macrophages to sites of tissue injury, suggesting that it might promote the progression of atherosclerosis (6, 7). Chemerin increases muscle insulin resistance by decreasing insulin-stimulated glucose uptake, and muscle insulin sensitivity is enhanced in chemerin-deficient mice; this suggests that chemerin itself has a role in insulin activity (8–10). Involvement of chemerin in the cardiovascular system becomes increasingly important with discoveries that chemerin stimulates angiogenesis (11) and might promote atherosclerosis (12, 13). Furthermore, serum chemerin levels were significantly associated with aortic stiffness in healthy individuals (14). However, there were conflicting data regarding the relationship between serum chemerin levels and atherosclerosis and diabetes (15–19). Additionally, none of the studies particularly assessed the link between serum chemerin levels and atherosclerosis in prediabetes.

Carotid intima–media thickness (CIMT), arterial stiffness, and epicardial fat thickness are useful non-invasive markers of subclinical atherosclerosis (20, 21). Brachial artery pulse wave velocity (baPWV) is the gold-standard measure of arterial stiffness and has been shown to be an independent predictor of

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cardiovascular mortality in various populations (22–25). Epicardial fat is a special fat depot that is related to visceral fat rather than total adiposity and shares the same microcirculation with myocardial tissue (26). Epicardial fat thickness (EFT) is associated with cardiovascular risks in patients with metabolic syndrome (27).

Therefore, in this study, we aimed to evaluate the association of serum chemerin level with non-invasive markers of subclinical atherosclerosis as exemplified by baPWV, CIMT, EFT, and carotid plaque presence, particularly in prediabetes and diabetes.

Methods

Subjects

We enrolled eighty age-, body mass index (BMI)-, and gender-matched participants [30 with type 2 diabetes mellitus (T2DM), 25 with prediabetes, and 25 with normal glucose tolerance (NGT)] aged 18–65 years who were admitted to endocrinology outpatient clinic in this cross-sectional study. T2DM and prediabetes were defined according to current guidelines of American Diabetes Association (28). Prediabetes was defined as impaired fasting glucose (serum glucose level, 100–125 mg/dL) and/or impaired glucose tolerance (second hour glucose response to oral glucose load, 140–199 mg/dL). Patients with malignancy, renal or hepatic disease, acute or chronic infection, rheumatologic disorder, vasculitis, and any clinical cardiovascular disease (myocardial infarction, stroke, unstable angina, peripheral artery disease, and revascularization) were excluded. None of the participants were cigarette smokers. The study protocol was approved by the University Local Ethics Committee and was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Study protocol

Anthropometric measurements, biochemical analysis of lipid parameters, fasting glucose level, fasting insulin level, serum chemerin level, ultrasonographic evaluation of CIMT, carotid plaque presence, epicardial fat thickness, and baPWV were determined. Waist circumference (WC) was measured at the midpoint between the lower border of the rib cage and the iliac crest. Hip circumference was measured at the largest point, and waist-to-hip ratio was calculated. BMI was calculated as kg/m^2. Total body fat percentage was determined with a bioelectric impedance analysis (BIA) system (Tanita BC-418 MA type segmental body analysis monitor; Tanita Corporation, Tokyo, Japan). Blood pressure (BP) was measured after 15 min of resting using an automated digital sphygmomanometer (Omron Healthcare, Kyoto, Japan) in the supine position, and the average of the measurements from both arms was considered.

Assessment of CIMT

CIMT was measured by a single experienced cardiologist who was blinded to the clinical data of the participants. CIMT is defined as the distance between the media–adventitia interface and the lumen–intima interface. Measurements were performed using a duplex ultrasound system with a 10-MHz scanning frequency in the B-mode, pulsed Doppler mode, and color mode using Vivid 5 (GE Vingmed, Horten, Norway). CIMT was measured at the far wall of the right and left common carotid arteries 10–20 mm proximal to the carotid bulb. The mean of five measurements on each artery was recorded. The reproducibility of the CIMT measurements was examined by conducting another scan 1 week later on 10 patients. In our laboratory, the intra-observer variability is below 10% for CIMT (4.7±1.9%), demonstrating good reproducibility. Carotid plaques were searched on the common, internal, and external carotid arteries. We defined presence of carotid plaque as intima–media thickening >1.0 mm. CIMT was always performed at plaque-free regions.

Assessment of epicardial fat thickness

EFT was measured by a single experienced specialist (U.C.) blinded to the clinical data of the patients. EFT thickness was measured from parasternal long-axis view at end-systole, along the mid-line of the ultrasound beam and parallel to the aortic valve annulus plane that was used as an anatomic marker (29). The maximum thickness of epicardial fat at any site was measured. To assess the reproducibility of EFT measurements, echocardiograms of randomly selected 10 patients were repeated by two independent physicians 24 hours after the index examination. The intra- and inter-observer intraclass correlation coefficients for EFT were 0.940 and 0.924, respectively ($p<0.001$). Using the Bland–Altman method, the mean difference between intra-observation and inter-observation were 3.1% (0.21±0.06) and 3.9% (0.26±0.09), respectively, indicating good reproducibility.

Assessment of arterial stiffness parameters

Subjects were instructed not to eat anything and drink alcohol, coffee, or tea for at least 12 h prior to the measurements. The test of arterial stiffness was performed in the supine position in a quiet, temperature-controlled room (22–24°C) in the early morning hours. Measurements were carried out by using a Mobil-O-Graph arteriograph system (Mobil-O-Graph NG, Stolberg, Germany). This system detects signals from the brachial artery even though cuff pressure is 35 mm Hg higher than the systolic pressure in the brachial artery. This technique is based on the fact that the contraction of the myocardium initiates a pulse wave (early systolic peak) running down in the aorta. This first wave is reflected from the aortic wall at the distal branching point and causes a reflected second wave (late systolic peak). The morphology of this second reflected wave depends on the stiffness of the large artery. By using amplitude and time difference of first and second waves, baPWV is calculated according to current guidelines (30). The Mobil-O-Graph NG software package allows us to automatically calculate aortic PWV (31). We performed arterial stiffness measurements once for each subject.

Laboratory analysis and assays

Blood samples were obtained after an overnight fast in the early morning between 8:00 and 10:00 am. The sera of the centrifuged blood samples at 4000 rpm for 20 min were stored at –80°C until assayed. Triglycerides, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using enzymatic calorimetric kits with intra- and inter-assay coefficients of variation (CV) of <10% (Roche Diagnostics GmbH, Mannheim, Germany). Fasting plasma glucose (FPG) was measured by the glucose oxidase method (Olympus AU 2700; Olympus America Inc., Melville, NY, USA). Insulin levels were measured by immunoradiometric assay (IRMA) method (Diasource, Louvain, Belgium). Serum chemerin levels were determined by enzyme-linked immunosorbent assay method (Biovendor, Brno, Czech Republic). The average intra- and inter-assay CV for chemerin were 6.0% and 7.6%, respectively. Homeostatic model assessment for insulin resistance (HOMA-IR) were calculated according to the formula [glucose (mg/dL) × insulin (μIU/mL)/405] (32).

Statistical analysis

Statistical analyses were carried out using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA). Differences between means were analyzed by one-way ANOVA and Kruskal–Wallis test according to the normality of distribution evaluated by Kolmogorov–Smirnov test. When performing correlation and regression analysis, non-normally distributed continuous variables were log-transformed. Correlation analysis was performed with Pearson's correlation test. After adjusting for age, gender, and BMI, Pearson's correlation coefficients and partial correlations were calculated to evaluate relationship between subclinical atherosclerosis markers, serum chemerin, glucose metabolism-related markers, and lipid profiles. In order to understand the effect of chemerin on subclinical atherosclerosis markers among the diabetes, prediabetes, and control groups, analysis of covariance (ANCOVA) was performed and adjusted for the confounding variables. The independent risk factors for baPWV, epicardial fat thickness, CIMT, and carotid plaque were determined by linear and/or multiple logistic regression analysis in the overall study group. The results are expressed as mean±standard deviation or median (interquartile range), and $p<0.05$ was accepted as statistically significant.

Results

Clinical and biochemical features of the study population are shown in Table 1. The medication history of the patients was

Table 1. Clinical and biochemical features of the study population

	Control n=25	Prediabetes n=25	Diabetes n=30	*P*
Age, years	46.8±9.8	47.6±6.9	49.6±7.8	0.459
Male/female, n/n	5/20	5/20	7/23	0.940
Weight, kg	76.7±11.9	82.2±15.5	78.0±13.1	0.324
BMI, kg/m^2	29.7±4.5	31.5±4.8	31.0±5.5	0.386
Waist to hip ratio	0.88±0.08	0.93±0.11	0.91±0.09	0.194
Chemerin, ng/mL	226.7±25.8	236.1±42.4	233.5±40.4	0.653
PWV, m/sec	6.6 (5.9–7.7)	6.9 (6.6–7.4)	7.4 (6.6–8.4)	0.023
Epicardial fat, mm	0.47±0.14	0.49±0.11	0.51±0.16	0.543
CIMT, mm	0.72±0.07	0.73±0.13	0.80±0.17	0.118
Plaque, n	3	3	11	0.035
Total body fat percentage, %	33.9±6.4	34.5±8.4	31.4±9.5	0.347
Fasting glucose, mg/dL	89.1±6.7	102.3±7.7	117.8±30.5	<0.001
Fasting insulin, μIU/mL	12.3±4.9	17.2±8.0	17.1±8.2	0.034
HOMA-IR	2.52 (1.96–3.15)	3.95 (3.27–4.78)	3.94 (3.94–6.45)	0.004
HbA1c, %	5.4 (5.2–5.6)	5.5 (5.4-6.2)	6.1 (5.7–7.4)	<0.001
Total cholesterol, mg/dL	189.3±36.0	210.8±39.2	183.0±41.0	0.018
Triglyceride, mg/dL	133.5 (71–194.5)	155.5 (113.8–182)	140 (95.5–192.3)	0.532
LDL-C, mg/dL	114.3±28.3	140.8±36.4	111.6±41.8	0.008
HDL-C, mg/dL	52.2±16.1	51.8±13.4	50.0±19.6	0.712

Data are presented as means±standard deviations (SD) or median (interquartile range) according to normality of distribution. Statistical analyses were performed using one-way ANOVA and/or Kruskal-Wallis test according to the normality of distribution
BMI - body mass index; CIMT - carotid intima-media thickness; HDL-C - high density lipoprotein cholesterol; HOMA-IR - homeostatic model assessment for insulin resistance; LDL-C - low density lipoprotein cholesterol; PWV - pulse wave velocity; TG - triglyceride

as follows. In the NGT group, five patients were on statins and two on antihypertensives; in the prediabetes group, five were on statin and five on antihypertensives; in the diabetes group, eight were on statin, thirteen on antihypertensives, and 24 on oral hypoglycemic agents. Among the groups, use of antihypertensive medication were significantly different (p=0.009); diabetes patients were more on antihypertensives than were prediabetes and control patients. None of the patients in the control and prediabetes groups were on hypoglycemic agents or metformin.

Serum chemerin levels were similar among the three groups (p=0.338). baPWV was significantly higher in diabetes patients than in prediabetes and NGT patients, but similar between the latter two (p=0.023) (Table 1). Additionally, carotid plaque presence was significantly higher in T2DM patients than in prediabetes and NGT patients (p=0.035). CIMT and epicardial fat thickness were not significantly different between groups. Analysis of glucose metabolism markers showed that plasma glucose (89.1±6.7, 102.3±7.7, 117.8±30.5; p<0.001), hemoglobin A1c (5.4±0.3, 5.7±0.5, 6.5±1.1; p<0.001), and HOMA-IR (2.70±1.06; 4.37±2.05, 5.38±2.41; p=0.004) increased significantly in a stepwise manner in the control, prediabetes, and diabetes patients, respectively. Total cholesterol and LDL-C were higher in prediabetes patients than in diabetes and control patients. More patients were on statins in the diabetes group (n=8) than in the prediabetes and control groups (n=5 each), but this difference did not reach a significance (p=0.790).

Chemerin levels were not correlated with baPWV, CIMT, and epicardial fat thickness overall (Fig. 1) as well as in the subgroups. Correlations of chemerin with clinical and metabolic parameters are shown in Table 2. Overall, chemerin levels were positively correlated with BMI, WC, total body fat percentage, triglyceride, systolic BP, and diastolic BP. Chemerin was significantly correlated with BMI and total body fat percentage in the control group; with BMI only in the prediabetes group; and with WC, BMI, total body fat percentage, systolic BP, and diastolic BP in the diabetes group. Correlations between chemerin and TC, LDL-C, triglyceride in diabetes were at the border of significance. After adjusting for age and gender, the correlations between serum chemerin and BMI in prediabetes and between chemerin and diastolic BP in diabetes were lost, and all other correlations remained significant. However, after adjusting for age, gender, and BMI, only the correlations between chemerin and systolic BP in diabetes patients and in overall study population were significant.

In order to understand the effect of chemerin on baPWV, epicardial fat thickness, and CIMT among the groups, we performed ANCOVA. Without any adjustment, only baPWV were different among the groups, as mentioned earlier. However, chemerin had no effect on these parameters (all p>0.05). Adjustment for age, gender, and BMI revealed no change, and further adjustment for presence of hypertension, use of antihypertensive medication, and statin also made no difference.

We created a model including age, sex, BMI, HOMA-IR, systolic BP, diastolic BP, TC, LDL-C, triglyceride, HDL-C, and chemerin to predict to the independent risk factors for baPWV, EFT, CIMT, and carotid plaque by linear and/or multiple logistic regression analysis in overall study population. Chemerin was not detected to be a risk factor for all the assessed subclinical atherosclerosis markers (Table 3). Age was found to be predictor for baPWV, CIMT, and carotid plaque; BMI for EFT; and gender for baPWV (all p<0.05).

Discussion

In the present study, we investigated whether serum chemerin had any association with markers of atherosclerosis, particularly in diabetes and prediabetes. We could not detect any association of serum chemerin levels with markers of subclinical atherosclerosis—CIMT, EFT, baPWV, and carotid plaque presence.

Accumulated data so far have been suggestive of assigning a role to chemerin in atherosclerosis, but evidences from several studies have been conflicting. A study conducted by Xiaotao et al. (19) comparing serum chemerin levels between patients with and without coronary artery disease (CAD) who underwent coronary angiography has found significantly increased chemerin levels in the patients with CAD; elevated chemerin level was an independent predictive marker for the presence of CAD. Similarly, a study by Hah et al. (33) found a positive correlation of chemerin with coronary artery stenosis in patients with documented CAD and chemerin levels were higher in multiple stenotic vessel group. Gu et al. (34) have recently showed that chemerin is associated with early atherosclerotic changes in essential hypertensive patients,

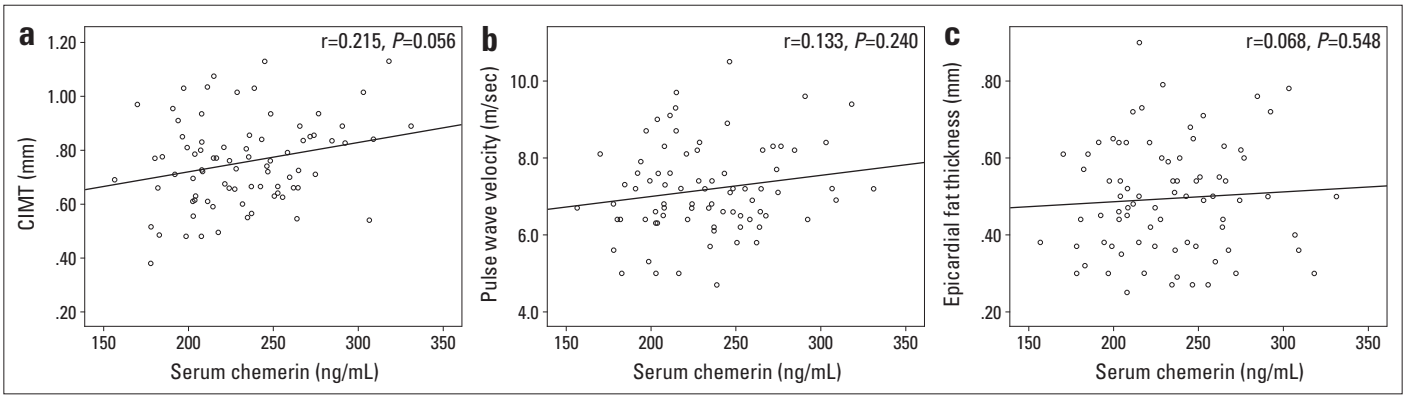

Figure 1. Pearson's correlation analysis of chemerin levels with carotid intima–media thickness, epicardial fat thickness, and pulse wave velocity

Table 2. Correlations of chemerin with clinical and metabolic parameters

	Control		Prediabetes		Diabetes		All subjects	
	P	***R***	***P***	***R***	***P***	***R***	***P***	***R***
Age	0.112	0.325	0.485	-0.147	0.327	0.185	0.300	0.117
Waist	0.084	0.352	0.445	0.168	**0.015**	**0.454**	**0.003**	**0.334**
BMI	**0.009**	**0.537**	**0.045***	**0.404**	**0.014**	**0.441**	**<0.001**	**0.447**
Body fat percentage	**0.007**	**0.537**	0.722	0.075	**0.013**	**0.450**	**0.004**	**0.319**
Glucose	0.551	0.125	0.802	-0.053	0.614	-0.096	0.966	-0.005
Insulin	0.810	0.051	0.262	0.233	0.369	0.173	0.121	0.176
HOMA-IR	0.713	0.077	0.314	0.210	0.523	0.124	0.170	0.156
HbA1c	0.206	0.281	0.725	-0.079	0.695	0.090	0.296	0.123
TChol	0.616	0.108	0.917	-0.022	0.075	0.030	0.141	0.167
LDL-C	0.777	0.060	0.263	-0.238	0.087	0.317	0.407	0.094
Triglyceride	0.516	0.136	0.212	0.2464	0.082	0.323	**0.035**	**0.240**
HDL-C	0.760	0.066	0.753	0.066	0.466	-0.138	0.752	-0.038
Systolic BP	0.183	0.282	0.884	0.031	**0.004****	**0.511**	**0.005****	**0.317**
Diastolic BP	0.089	0.354	0.855	0.404	**0.046***	**0.367**	**0.025**	**0.252**
Epicardial fat	0.866	0.035	0.702	0.081	0.751	0.060	0.548	0.068
CIMT	0.479	0.149	0.076	0.361	0.344	0.179	0.056	0.215
baPWV	0.204	0.200	0.495	-0.143	0.142	0.275	0.240	0.133

Correlation analysis was performed with Pearson correlation test. Non-normally distributed continuous variables were log-transformed
BMI - body mass index; BP - blood pressure; CIMT - carotid intima-media thickness; HDL-C - high density lipoprotein cholesterol; HOMA-IR - homeostatic model assessment for insulin resistance; LDL-C - low density lipoprotein cholesterol; PWV - pulse wave velocity; TG - triglyceride
*After adjustment for age and gender, the correlation was lost
**After adjustment for age, sex, and BMI, all correlations were lost except the correlation between systolic BP and chemerin overall and in the diabetes group

and Neves et al. (35) demonstrated that chemerin may influence vascular function through proinflammatory effects. Contrarily, in a study by Lehrke et al. (18), serum chemerin levels were determined in 303 patients with chest pain who underwent dual-source multi-slice CT-angiography. The authors reported that serum chemerin levels were not correlated with coronary plaque burden and the number of non-calcified plaques after adjustment for the cardiovascular disease risk factors (18). Our results are partly in accordance with their results (18), and differ from those by Xiaotao et al. (19) and Hah et al. (33). The discordant results might be in part due to the study population characteristics. We particularly excluded the patients with known CAD, whereas participants in the aforementioned studies had already documented CAD or had higher risks for cardiovascular diseases. Additionally, none of these studies has specifically addressed the association of chemerin and atherosclerosis markers in diabetes and prediabetes. Based on our observations, we cannot assume that chemerin might play a role in atherosclerosis.

Table 3. Relation of chemerin with subclinical atherosclerosis markers in regression analyses

	Beta coefficient	*P*
PWV	-0.031	0.767
CIMT	0.219	0.084
EFT	-0.046	0.740
Carotid plaque*	–	0.804

*Regression analysis for carotid plaque was performed using logistic regression since the dependent variable is categorical; other regression analyses were performed using multiple linear regression
Model included age, gender, BMI, HOMA-IR-systolic blood pressure, diastolic blood pressure, TC, LDL-C, HDL-C, TG, and chemerin
CIMT - carotid intima–media thickness; EFT - epicardial fat thickness; PWV- pulse wave velocity

Arterial stiffness is an independent predictor of all-cause and cardiovascular mortality in diabetes patients (25). In animal studies, altered arterial compliance precedes angiographically detectable atherosclerosis (36). Yoo et al. (14) examined the association between circulating chemerin levels and arterial stiffness as exemplified by the baPWV in apparently healthy individuals. What they found was that serum chemerin significantly associated with the baPWV, but not with CIMT, and that chemerin was an independent risk factor for arterial stiffness. In our study, we could not detect an association between serum chemerin levels and PWV either for patients with diabetes or controls. As the both studies included patients without known CAD, we would have expected such an association. We should note, however, that participants in the study by Yoo et al. (14) were drug-naive, but our study participants were either drug-naive or treated with antihypertensives, statins, or oral hypoglycemic agents.

Chemerin decreases insulin-stimulated glucose uptake in skeletal muscle cells, and muscle insulin sensitivity is enhanced in chemerin-deficient mice; this suggests that chemerin itself contributes to impaired insulin activity (8–10). However, in this study, we failed to detect a significant difference in the chemerin levels of patients with NGT, prediabetes, or diabetes. Bozaoğlu et al. (11) measured similar serum chemerin levels in NGT controls and type 2 diabetes patients. Furthermore, Bauer et al. (37) demonstrated that serum chemerin levels in healthy controls did not correlate with markers of insulin sensitivity, including fasting glucose, fasting insulin, or HOMA index, as observed in our study.

Chemerin is described as a biomarker for adiposity because circulating chemerin levels associate strongly with BMI (3). In our study, chemerin levels correlated strongly with BMI in all groups and body fat percentage correlated with chemerin levels in diabetes and control patients. Since chemerin levels were similar between groups based on glucose measures, it seemed that chemerin was mostly an indicator of obesity. Chemerin level also correlated with systolic and diastolic BP in patients diabetes, parallel to the reports from past studies (16). Chemerin has been pointed as an endogenous vasoconstrictor produced by both visceral and perivascular adipose tissue that modifies vascular tone via its receptor (38). In the previous studies, chemerin levels correlated with metabolic factors related to obesity, such as BMI, triglyceride levels, and BP (3).

Study limitations

Our study has several strengths and limitations. First, our study consisted of relatively small number of subjects. Second, our method of measurement of chemerin using ELISA measures prochemerin, chemerin, and likely some of the proteolytically processed short forms; in other words, measurement of the active form would provide a better insight.

Conclusion

In conclusion, our study showed that serum chemerin level is not a predictive marker for subclinical atherosclerosis in prediabetes and diabetes, but chemerin correlates well with key aspects of the metabolic syndrome, especially BMI, particularly in diabetes. Further large-scale, prospective studies are needed to elucidate the role of chemerin in subclinical atherosclerosis in populations with diabetes and prediabetes.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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