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Relationship of Serum Chemerin Concentrations with Coronary Slow Flow: A Pathophysiological and Clinical Analysis

Aim	Coronary slow flow (CSF) is a condition characterized by below normal blood flow in coronary arteries without significant coronary stenosis. Its pathophysiology is unclear but may involve inflammation, endothelial dysfunction, and microvascular impairment. Chemerin, an inflammation-related adipokine, has been proposed as a potential biomarker in CSF. This study examines the relationship between serum chemerin concentrations and CSF.
Material and methods	A total of 100 patients who underwent coronary angiography were classified into CSF (n=50) and normal coronary flow (NCF, n=50) groups. Coronary flow rates were assessed using the Thrombolysis in Myocardial Infarction Frame Count (TFC) method. Serum chemerin concentrations were measured by ELISA. Logistic regression, correlation, and ROC analyses were performed to identify predictors of CSF and to evaluate diagnostic performance.
Results	Chemerin concentrations were significantly higher in the CSF group ($p<0.001$). Logistic regression identified chemerin as an independent CSF predictor (OR=1.097; 95% CI: 1.022–1.177; $p=0.005$). Chemerin concentrations correlated positively with TFC ($r=0.713$, $p<0.001$). A chemerin cutoff value of 124.5 ng/ml provided 88% sensitivity and 80% specificity for CSF diagnosis.
Conclusion	Elevated serum chemerin is associated with CSF, suggesting its role in the pathogenesis of CSF and its potential as a diagnostic biomarker. Further research is needed to explore chemerin-targeted therapies in patients with CSF.

Keywords	Endothelial dysfunction; inflammation; TIMI frame count; cardiovascular biomarker
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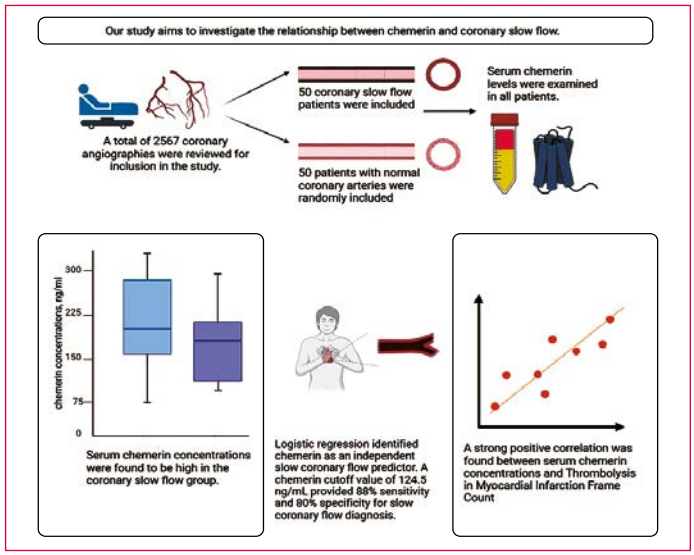
Introduction

CSF is a clinical condition characterized by slow blood flow in the epicardial coronary arteries as observed angiographically but without significant coronary stenosis. CSF is commonly associated with myocardial ischemia and chest pain, and CSF is considered a significant risk factor for cardiovascular mortality and morbidity [1]. However, the underlying pathophysiological mechanisms of CSF have not been fully elucidated, although processes such as inflammation, microvascular dysfunction, and endothelial dysfunction are thought to play a role [1–5].

Chemerin is an adipokine that plays a role in inflammation and metabolic processes [6]. and has also been shown to have regulatory effects on the vascular system [6]. Recent studies have shown that chemerin concentrations may be associated with cardiovascular diseases and can be used as a marker of inflammatory processes [6–9]. However, the role and clinical significance of chemerin concentrations in the pathogenesis of CSF have not yet been fully established [6]. Chemerin has

Central illustration. Relationship of Serum Chemerin Concentrations with Coronary Slow Flow: A Pathophysiologicaland Clinical Analysis



been suggested as a potential link between obesity and Type 2 Diabetes Mellitus (T2DM) [9]. Studies have shown that plasma chemerin concentrations are positively associated with body mass index, fasting serum insulin, fasting blood glucose, plasma triglycerides, and total serum cholesterol, and negatively associated with high-density lipoprotein [10].

This study aimed to compare serum chemerin concentrations between patients with CSF and individuals with normal coronary flow. In this context, it was hypothesized that potential differences in chemerin concentrations could shed light on the pathogenesis of CSF, and that chemerin might have a potential role in the diagnosis and treatment of CSF.

Material and methods

Study population

This study initially included 2568 patients who underwent coronary angiography between August 2020 and February 2021 due to clinical suspicion of myocardial ischemia based on exercise stress testing or myocardial perfusion scintigraphy. Of these patients, 100 were classified into two groups: patients with CSF (CSF group, n=50) and patients with normal coronary flow (NCF group, n=50). Angiographic criteria for identifying CSF are described below.

Detailed medical histories and comprehensive physical examinations were performed for all participants. Additional assessments included twelve-lead electrocardiography and transthoracic echocardiography conducted by two independent specialists. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medication. Diabetes mellitus was diagnosed in cases with fasting blood glucose concentrations ≥126 mg/dl or ongoing treatment with antidiabetic drugs. Hyperlipidemia was identified as a total cholesterol ≥200 mg/d or a history of statin use, excluding the last three months. Patients who smoked prior to hospital admission were categorized as smokers.

Exclusion criteria included the presence of coronary artery disease, acute coronary syndrome, peripheral arterial disease, congestive heart failure (ejection fraction <55%), a history of cardiovascular procedures, stroke, pulmonary hypertension, valvular heart disease, cardiomyopathy, myocarditis, pericarditis, hepatic dysfunction, severe renal disease (estimated glomerular filtration rate <15 ml/min/1.73 m^2), chronic inflammatory conditions, malignancies, active infections, or endocrine/metabolic disorders other than diabetes mellitus. Patients using corticosteroids, antioxidant vitamins, or alcohol were also excluded. During angiography, patients who developed vasovagal reactions following puncture, with blood pressure dropping below 90/60 mmHg on monitoring and experiencing bradycardia, were excluded from the study as they could cause a false picture of CSF.

The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants. The research adhered to the principles outlined in the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

Coronary angiography

Coronary angiography was conducted using the Judkins technique by two experienced cardiologists who were blinded to the clinical data of the patients. Iohexol, a non-ionic contrast agent, was administered manually at a rate of 6–10 ml per injection, and coronary arteries were visualized on standard planes. Coronary flow rates were assessed using the Thrombolysis In Myocardial Infarction Frame Count (TFC) method as defined by Gibson et al [11].

For the TFC analysis, the left anterior descending (LAD) and circumflex (Cx) arteries were evaluated using caudal angulations in the right anterior oblique projection or cranial angulations in the left anterior oblique projection. The first frame was defined as the frame where concentrated dye fully filled the proximal coronary artery lumen, touching both edges, with forward movement visible. The final frame was recorded when the contrast column's edge reached the distal landmark. Specific landmarks were the mustache segment for the LAD, the distal bifurcation for the Cx, and the first branch of the posterolateral artery for the RCA [11].

For the LAD artery, the TFC was adjusted by dividing the final count by 1.7 to account for its longer length. The normal visualization time differed among the coronary arteries, since the LAD is longer than the other epicardial coronary arteries, LAD TFC was divided by 1.7 with corrected cut-off frame counts of 36.2±2.6 for LAD, 22.2±4.1 for Cx, and 20.4 ±3.0 for RCA. Below these values were defined as slow CSF by Gibson et al. [11]. Patients were categorized as having CSF if their TFC exceeded two standard deviations above the normal range for at least two arteries. The mean TFC was calculated by averaging the TFC values for LAD, Cx, and RCA [11].

Laboratory measurements

Blood samples were collected from the antecubital vein upon patient admission. Routine laboratory tests included measurements of serum creatinine, white blood cell (WBC) count, platelet count, and hemoglobin concentrations. Lipid profiles and other biochemical parameters were determined using standard laboratory methods. Blood samples from the patients to be included in the study groups were collected the next morning after hospitalization, in a fasting state, before discharge.

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Table 1. Baseline characteristics, laboratory findings, TFC and chemerin levels of the study groups (n=100)

Variables	Patients with NCF(n=50)	Patients with CSF(n=50)	p value
Age, yrs	54.1 ± 14.1	57.7 ± 7.4	0.102
BMI, kg/m^2	27.4 ± 3.7	27.0± 3.4	0.551
Female	25 (50.0)	25 (50.0)	
Diabetes Mellitus	12 (24.0)	23 (46.0)	0.021
Hypertension	12 (24.0)	22 (44.0)	0.035
Dyslipidemia	25 (50.0)	28 (56.0)	0.548
Family history	8 (11.0)	11 (22.0)	0.444
Smoking	10 (20.0)	19 (38.0)	0.047
Glucose, mg/dl	105.5 ± 30.4	128.1 ± 51.7	0.009
Creatinine, mg/dl	0.76 ± 0.18	0.87 ± 0.21	0.002
Uric Acid, mg/dl	5.7 ± 2.4	5.7 ± 1.9	0.768
WBC count, 10^3/mm^3	7.1 ± 2.1	7.4 ± 1.7	0.425
Hemoglobin, g/dl	13.4 ± 1.7	13.7 ± 1.5	0.255
Platelet count, 10^3/mm^3	248 ± 48	228 ± 60	0.107
Total cholesterol, mg/dl	201.4 ± 43.4	193.7 ± 41.3	0.365
Triglyceride, mg/dl	161.2 ± 75.7	160.7 ± 82.3	0.972
LDL-cholesterol, mg/dl	116.8 ± 36.0	113.3 ± 33.5	0.616
HDL-cholesterol, mg/dl	48.2 ± 11.8	44.2 ± 11.7	0.094
Hs-CRP, mg/l	3.1 (1.2- 4.6)	4.9 (2.5- 6.5)	0.030
LVEF, %	58.2 ± 4.6	58.9 ± 5.3	0.701
TFC-LAD	36.2 ± 7.4	53.2 ± 6.9	< 0.001
TFC-Cx	28.9 ± 5.8	39.4 ± 5.6	< 0.001
TFC-RCA	24.3 ± 5.1	34.5 ± 4.6	< 0.001
TFC-mean	29.8 ± 6.1	42.4 ± 5.6	< 0.001
Chemerin, ng/ml	84.6 ± 29.9	188.4 ± 67.5	< 0.001

Data are mean ± SD or number (percentage). BMI, body mass index; NCF, normal coronary flow; CSF, slow coronary flow; HDL, high density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricle ejection fraction; NCF, normal coronary flow; CSF, slow coronary flow; TFC, Thrombolysis in Myocardial Infarction Frame Count ; WBC, white blood cells.

Table 2. Multivariate logistic regression analysis to predict CSF

Variable	Univariable, OR (95% CI)	P value	Multivariable, OR (95% CI)	p value
Diabetes Mellitus	2.698 (1.148-6.341)	0.023	1.260 (0.011-139.585)	0.923
Hypertension	2.488 (1.057-5.857)	0.037	0.453 (0.051-4.030)	0.478
Smoking	7.818 (2.951-20.724)	< 0.001	2.473 (0.248-24.680)	0.441
Glucose	1.014 (1.003-1.026)	0.015	1.016 (0.982-1.051)	0.995
Creatinine	0.983 (0.970-0.995)	0.004	62.029 (0.303-12694.844)	0.128
Hs-CRP	3.485 (2.143-5.666)	< 0.001	2.071 (0.989-4.336)	0.049
Chemerin	1.126 (1.060-1.197)	< 0.001	1.097 (1.022-1.177)	0.005

CI, confidence interval;
Hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio

Serum chemerin concentrations (ng/ml) were measured using a Human Chemerin (CHEMERIN) ELISA kit (Hangzhou Eastbiopharm Co., Hangzhou, China). A Synergy 4 Microplate Reader (BioTek, USA) and a Multiwash Microplate Washer (TriContinent Scientific, USA) were used. Chemerin concentrations were calculated based on a standard curve derived using a four-parameter logistic equation, as recommended in the kit protocol.

Reproducibility of TFC

To evaluate intra-observer consistency, a random sample of 15 patients (7 TFC, 8 NCF) from the study group was chosen. Measurements were repeated under identical baseline conditions, and the reproducibility of the TFC was determined using the coefficient of variation between repeated measurements. The intra-observer variability for the TFC score was 2.5%.

Statistical Analysis

All statistical evaluations were performed using SPSS for Windows, version 19.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics are expressed as mean ± standard deviation (SD) for continuous variables and as numbers (percentages) for categorical data. The Kolmogorov-Smirnov test was used to assess the normality of data distributions. For comparisons of normally distributed continuous variables, the Student's t-test was applied, while the Mann-Whitney U test was used for non-normally distributed variables. Groups of categorical variables were compared with the Chi-squared test. Correlations between variables were analyzed using Pearson's correlation coefficient. Univariate and multivariate logistic logistic regression was conducted to identify the effects of independent variables, with results expressed as 95% confidence intervals (CI). Statistical significance was determined at a p value of <0.05.

Results

The baseline demographic, clinical characteristics and laboratory findings of the study participants are summarized in Table 1. There were no statistically significant differences between the CSF and NCF groups in terms of age, body mass index, gender distribution, dyslipidemia, or family history of cardiovascular diseases. However, the prevalence of diabetes mellitus (p=0.021), hypertension (p=0.035), and smoking (p=0.047) was significantly higher in the CSF group. Patients in the CSF group exhibited higher concentrations of serum glucose (p=0.009), creatinine (p=0.002), and high-sensitivity C-reactive protein (Hs-CRP) (=0.030) and chemerin (p<0.001) compared to controls, indicating a potential association between these markers and CSF.

Univariate logistic regression analysis revealed multiple factors that significantly heightened the risk of CSF

(Table 2). These factors were, diabetes mellitus, hypertension, smoking, higher serum glucose concentrations, serum creatinine concentrations, Hs-CRP, and serum chemerin concentrations. Multiple linear regression analysis found that Hs-CRP and chemerin concentrations were independent predictors of CSF (Table 2).

In the correlation analysis, TFC were negatively correlated with chemerin concentrations (p<0.001, r=0.713) (Figure 1). In linear regression analysis, chemerin concentrations and TFC were closely related. (OR=0.073, 95% CI: 0.054–0.092, p<0.001).

Receiver operating characteristic curve analysis showed that serum chemerin concentrations were a significant predictor for CSF (AUC=0.859; 95% CI=0.785–0.934; p<0.001). This analysis identified a cut-off value of 124.5 ng/ml for serum chemerin concentrations to estimate CSF, with a sensitivity of 88% and a specificity of 80% (Figure 2).

Figure 1. Correlation between serum chemerin level and TFC

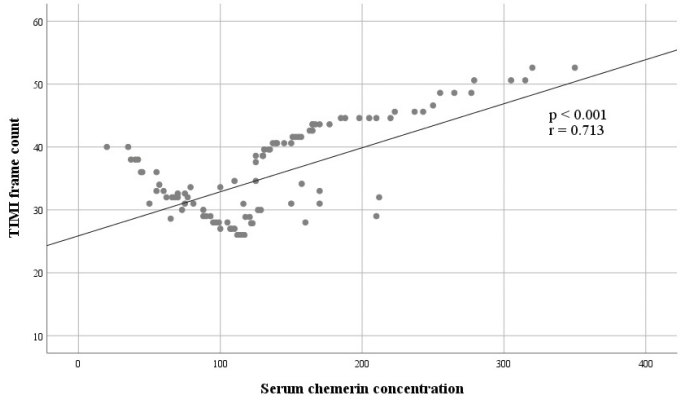
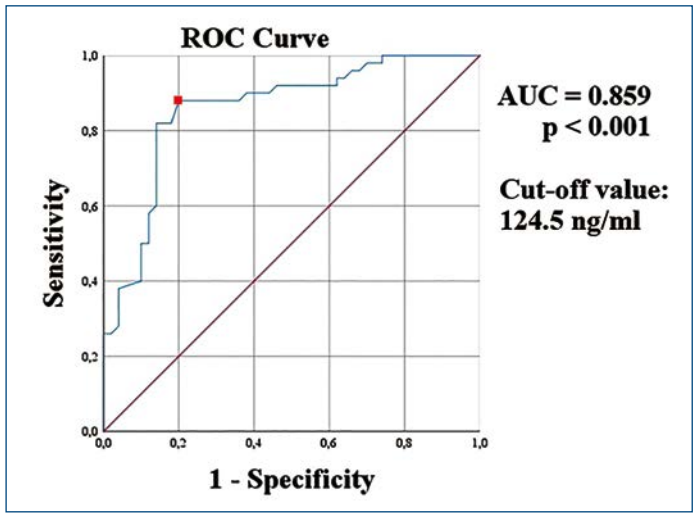


Figure 2. Receiver operating characteristics curve analysis of serum chemerin



Discussion

The pathophysiological mechanisms underlying primary CSF have not been previously elucidated fully, although some studies have investigated factors that may lead to CSF. Yücel et al. stated that medial hypertrophy, myointimal proliferation, endothelial degeneration associated with myofibrillar degenerative foci, and lipofuscin accumulations examined by electron microscopy are factors that may lead to endothelial dysfunction in CSF patients [12]. In addition, it has been suggested that coronary adrenergic hyperactivity, which develops due to increased sympathetic activity, may be a mechanism associated with decreased coronary blood flow and angina in these patients. Higher concentrations of adrenaline and noradrenaline were detected in CSF patients, supporting a potential role for increased adrenergic activation in the pathogenesis of CSF [13]. Kurtoglu et al [14] reported that improvements in microvascular tone and coronary flow were observed with the administration of microvascular vasodilators, indicating a functional increase in microvascular resistance in CSF patients. In addition, many studies have revealed that inflammation is an important factor in the development of CSF [13, 15].

Chemerin is an adipokine, i.e., a protein predominantly synthesized in adipose tissue. Chemerin plays a role in numerous biological processes, including adipogenesis, glucose metabolism, tumor formation, inflammation, angiogenesis, mitochondrial regulation, carbohydrate metabolism, appetite regulation, and immune cell migration [6, 16–18].

Increasing evidence suggests that chemerin plays numerous significant roles in the pathogenesis of cardiovascular diseases, acting as an adipokine, chemotactic agent, and growth factor. As an adipokine, chemerin regulates glucose and lipid concentrations, with mitochondrial regulation, thereby influencing lipid accumulation in the endothelium and the progression of atherosclerosis [19, 20]. Even prior to the onset of atherosclerosis, pre-atherosclerotic alterations in the vascular wall can disrupt vascular stiffness equilibrium, which is thought to be among the pathophysiological changes contributing to the development of CSF [13]. Additionally, the CMKLR1 receptor, which interacts with chemerin, is located in vascular endothelial and smooth muscle layers. This receptor pathway has been found to increase vascular smooth muscle tone, which is one of the contributing factors to CSF [13, 21].

Chemerin has been shown to reduce nitric oxide (NO) – mediated vascular relaxation and cyclic guanosine monophosphate (cGMP) formation, as demonstrated by Neves et al. [22]. NO is one of the most critical molecules in determining flow dynamics within endothelial cells, and its deficiency creates a predisposition to the development of CSF [13]. The balance of NO in endothelial cells is maintained by endothelial nitric oxide synthase (eNOS),

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Каждый 5-й пациент перенесет повторный инфаркт миокарда

в течение года после первого события[1].

Достижение целевого уровня ХС ЛНП — ключ к улучшению прогноза пациента. Пациент не узнает об этом без вашей рекомендации.

<1,4 ммоль/л и снижение ⩾50% от исходного

Достижение целевого уровня ХС ЛНП

8 (±4) недель

Контроль липидного профиля – через 8 (±4) недель после начала терапии и интенсификация терапии при недостижении целевого уровня ХС ЛНП

Если у пациента, перенесшего ИМ, при использовании максимально переносимой дозы статина в сочетании с эзетимибом концентрация ХС ЛНП в крови остаётся выше целевого уровня, рекомендуется добавить инклисиран или ингибитор PCSK9 для дополнительного снижения уровня ХС ЛНП в крови и риска ишемических событий[2,3].

Больше полезных материалов для врачей — в канале «Кардиогид». Подписывайтесь!

ХС ЛНП — холестерин липопротеинов низкой плотности; ИМ — инфаркт миокарда.

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and chemerin has been found to directly reduce eNOS synthesis and stimulate NO degradation [13].

The in vitro administration of chemerin to vascular smooth muscle cells has been shown to activate the endothelin-1-dependent pathway, which plays a role in the short-term pathophysiology of CSF [23, 24]. This lead to smooth muscle proliferation and endothelial dysfunction, while long-term incubation resulted in the apoptosis of smooth muscle cells. These findings suggest that chemerin may exert different functions at various stages of vascular remodeling and dysfunction

Increased secretion of chemerin from endothelial tissue has been observed to enhance vascular inflammation and promote the expression of mediators such as CRP, TNF-α, and IL-6, which lead to increased monocyte and lymphocyte migration to endothelial cells [25]. Additionally, these mediators increased CMKLR1 expression in endothelial cells. This cascade triggered a process that leads to a chronic decline in endothelial functions [25]. Increased chemerin circulation has been associated with elevated synthesis of intercellular adhesion molecule-1 (ICAM-1) and E-selectin in human coronary artery cells, which are key contributors to vascular endothelial dysfunction [26]. It can be suggested that inflammation is associated with many effects of chemerin on endothelial dysfunction that would lead to CSF. In the current study, consistent with the literature, HsCRP concentrations and chemerin concentrations increased correlatively in the CSF group.

Increased chemerin concentration is associated with elevated reactive oxygen species (ROS) in vascular endothelial cells, and heightened oxidative stress plays a significant role in the pathophysiology of CSF [13, 26]. Shen et al. found that chemerin administration to human aortic endothelial cells increased mitochondrial ROS production, while the infusion of the antioxidant N-acetylcysteine or suppression of the CMKLR1 receptor reduced ROS production [27].

CSF has been considered a precursor of atherosclerotic heart disease [28]. Significant reductions in cardiovascular mortality and morbidity have been achieved through the inhibition of the platelet aggregation pathway, interventional treatments, and therapies targeting the cholesterol mechanism [28]. However, despite all current treatments, atherosclerosis remains one of the leading causes of death worldwide [28, 29]. This has lead to new therapies aimed at preventing inflammation and ROS damage, which are critical steps in the pathophysiology of CSF and atherosclerosis [28]. The growing body of evidence regarding the role of chemerin in cardiovascular diseases has suggested that targeting its pathway could serve as a basis for developing therapeutic agents. One of the most extensively studied agents in this regard is CCX832, an inhibitor of the CMKLR1 pathway affected by chemerin.

In this context, one of the most extensively studied compounds is the CMKLR1 inhibitor CCX832, which has been shown to significantly improve chemerin-induced vascular dysfunction both in vitro and in vivo [25]. Research has found that chemerin-induced vascular inflammation in microvascular endothelial cells is reduced by CCX832, and microvascular dysfunction is thought to play a significant role in the pathogenesis of CSF [13, 30]. Additionally, CCX832 has been demonstrated to have an inhibitory effect on the abnormal contraction of human pulmonary and coronary arteries [31, 32], and it has been shown to mitigate ROS damage in aortic smooth muscle cells [30]. The promising potential of the CCX832 molecule has paved the way for the identification and development of other CMKLR inhibitors. Resolving E1, which binds to another ligand of the CMKLR1 receptor, is a derivative molecule produced from omega-3 fatty acids. Studies reported in the literature have shown that RvE1 reduces vasoconstriction, decreases vascular calcification, improves endothelial dysfunction, reduces ROS damage, and exhibits strong vascular anti-inflammatory properties [32].

Limitations of the study

Firstly, this study has a relatively small number of subjects. Secondly, long-term mortality and morbidity follow-up data were are not available. Intravascular ultrasound or optical coherence tomography methods were not utilized; only coronary angiographic evaluation was performed, which may have missed minor atherosclerotic changes. It would be beneficial to support the findings of our study with long-term, multicenter studies.

Conclusion

A relationship between CSF and chemerin was demonstrated for the first time. Thus, therapies developed based on the mechanism of action of chemerin might to be effective in the treatment of CSF. The findings of this study should stimulate new research to support the hypothesis that chemerin is a critical factor in the development of CSF.

Ethics statement and Data availability

Our study was approved by the decision of the local Clinical Research Ethics Committee. Data will be made available on request.

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No conflicts of interest are reported.

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