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ARTICLE

Increased serum chemerin levels associated with carotid intima-media thickness

Aumento dos níveis séricos de chemerin associados à espessura das camadas intima-media carotídea

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ABSTRACT

Background: Elevated levels of chemerin can predict future ischemic cerebrovascular disease. Although chemerin is thought to play a role in atherosclerotic inflammation, whether circulating chemerin levels are associated with the severity of atherosclerosis remains to be determined. **Objectives:** Through the use of carotid Doppler ultrasonography, our aim in this study was to investigate the relationships of serum chemerin levels with carotid intima-media thickness (CIMT) as an indicator of generalized atherosclerosis. **Methods:** This study compared 40 patients with ischemic stroke and 40 healthy subjects. Measurements were made at end-diastole using color Doppler ultrasonography (CDUS) after a 5-min rest interval in a quiet and dark room. CIMT was defined as the distance between the innermost edge of the luminal echo to the innermost edge of the media/adventitia echo. CIMT was measured in the posterior wall of both common carotid arteries within 1 cm proximally to the bulbus. Three measurements were made on both sides and the average measurement was taken as the CIMT. Serum chemerin levels were determined in all patients and healthy subjects. **Results:** Serum chemerin levels were significantly higher in the patient group than in the control group ($p=0.004$). Serum chemerin levels were positively correlated with CIMT ($p<0.05$). There was a significant difference between the groups with regard to CIMT ($p<0.001$). **Conclusion:** Elevated serum chemerin levels appear to be associated with CIMT, thus suggesting that a link exists between chemerin and atherosclerotic ischemic cerebrovascular disease.

Keywords: Chemerin Protein; Stroke; Carotid Intima-Media Thickness.

RESUMO

Introdução: Níveis elevados de chemerin podem prever doenças cerebrovasculares isquêmicas futuras. Embora se acredite que a chemerin desempenhe um papel na inflamação aterosclerótica, ainda não foi determinado se os níveis circulantes de chemerin estão associados à gravidade da aterosclerose **Objetivos:** Por meio do uso da ultrassonografia Doppler da carótida, nosso objetivo neste estudo foi investigar as relações dos níveis séricos de chemerin com a espessura da íntima-média da carótida (EIMC) como um indicador de aterosclerose generalizada. **Métodos:** Este estudo comparou 40 pacientes com AVC isquêmico e 40 indivíduos saudáveis. As medidas foram feitas no final da diástole usando ultrassonografia Doppler em cores (USDC), após um intervalo de descanso de 5 minutos em um quarto silencioso e escuro. A EIMC foi definida como a distância entre a borda mais interna do eco luminal e a borda mais interna do eco da mídia/adventícia. EIMC foi medido na parede posterior de ambas as artérias carótidas comuns dentro de 1 cm proximalmente ao bulbo. Três medições foram feitas em ambos os lados e a medição média foi tomada como o EIMC. Os níveis séricos de chemerin foram determinados em todos os pacientes e indivíduos saudáveis. **Resultados:** Os níveis séricos de chemerin foram significativamente maiores no grupo de pacientes do que no grupo controle ($p=0,004$). Os níveis séricos de chemerin foram positivamente correlacionados com EIMC ($p<0,05$). Houve diferença significativa entre os grupos em relação à EIMC ($p<0,001$). **Conclusão:** Níveis séricos elevados de chemerin parecem estar associados com a EIMC, sugerindo que existe uma ligação entre chemerin e doença cerebrovascular isquêmica aterosclerótica.

Palavras-chave: Chemerin; Acidente Vascular Cerebral; Espessura Intima-Media Carotídea.

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INTRODUCTION

Ischemic cerebrovascular diseases are mainly of atherosclerotic origin[1,2]. Patients with atherosclerosis or those at high risk of atherosclerosis are likely to present accompanying chronic low-intensity inflammation. A local or systemic flare-up of the inflammatory process may result in acute clinical events, and this plays a major role in atherothrombosis[3]. Macrophages and T lymphocytes are inflammatory cells that accumulate in the atherosclerotic arteries. These cells, together with adhesion molecules and cytokines expressed from dysfunctional endothelium, result in atherosclerotic plaques in the corresponding artery beds. This becomes sensitive and rupture-prone, thereby providing a basis for ischemic stroke[4,5].

Adipokines released from adipose tissue are one of the factors that contribute most to inflammatory stimuli. Because of their distinctive autocrine, paracrine and endocrine properties, they are considered to play a role in the pathogenesis of cardiovascular diseases and metabolic syndrome. Chemerin, also known as tazarotene-induced gene 2 protein (TIG2) or retinoid acid receptor responder 2 (RARRES2), is an adipokine with a significant role in inflammation. Chemerin acts as a ligand for chemokine-like receptor 1 (CMKLR1), which is expressed by various cells that play a role in inflammation. It also acts a chemoreactant that recruits immune cells towards the damage site[6,7,8].

The earliest event in the atherosclerotic process is the formation of fatty streaks in the intimal layer, followed by thickening of the intima-media layers[9,10,11]. In numerous experimental and cross-sectional studies, increased carotid intima-media thickness (CIMT) has been implicated as a valid index and early marker of atherosclerosis[12,13,14]. Moreover, CIMT is measured by color Doppler ultrasonography (CDUS) and there is a growing body of literature investigating the association between CIMT and various diseases including coronary artery disease, cerebrovascular disease (CVD), nephrotic syndrome, peripheral artery disease and migraine[15,16,17,18].

In this study, we aimed to investigate the relationship between the serum level of chemerin and CIMT.

METHODS

This was a prospective study in which 40 healthy subjects and 40 acute ischemic stroke patients were included. The signs and symptoms of acute ischemic stroke were ascertained within the first 48 h after the stroke. Patients who were admitted after the first 24 h or whose symptoms were completely resolved within 24 h were excluded from the study. The study protocol was approved by Firat University Medical School Clinical Research Ethics Board (approval date, June 24, 2011; No. 10). In patients who had acute focal neurological deficits lasting more than 24 h and had no apparent cause other than those of vascular origin, the diagnosis was established by means of a complete neuroradiological examination including brain computed tomography (CT) and/or cranial magnetic resonance imaging (MRI) scans.

Patients' records were analyzed to identify the proven risk factors for acute ischemic stroke, including hypertension (systolic blood pressure [SBP]>140 mmHg and diastolic blood pressure [DBP]>90 mmHg), diabetes mellitus (DM) (fasting blood glucose [FBG] 70–105 mg/dL) and dyslipidemia; and also to identify the medications used by the patients. Physical and neurological examinations, body weight and height measurements, complete blood count (CBC), liver, kidney and thyroid function tests, electrocardiogram (ECG), measurement of electrolytes and lipid profiles, CT, cranial MRI and diffusion MRI were performed for each subject. CIMT was measured using CDUS. To assess chemerin concentrations, SBP, DBP and FBG levels were measured during blood collection. Normal levels of serum low-density lipoprotein (LDL) and triglyceride were accepted as <130 and <180 mg/dL, respectively.

For the assessment of CIMT, the subject was placed in the supine position with the head rotated 15–45 degrees towards the opposite side and tilted slightly. The measurements were made at end-diastole using CDUS after a 5-min rest interval in a quiet and dark room. CIMT was defined as the distance between the innermost edge of the luminal echo to the innermost edge of the media/adventitia echo. Carotid arteries were studied using a 7–14 MHz linear transducer (Toshiba Aplio XG, Tokyo, Japan). All the measurements were performed by the same radiologist. Optimal longitudinal images were frozen and stored for offline analysis. CIMT was measured in the posterior wall of bilateral common carotid arteries within 1 cm proximally to the bulbus. Three measurements were made on both sides and the average measurement was taken as the CIMT. A CIMT of above 1 mm was considered pathological (Figures 1A and 1B).

Body weight and height were recorded for each subject and body mass index (BMI) was calculated using the following formula: BMI=body weight (kg)/height (m)^2. A BMI of 30 kg/m^2 or higher was considered to indicate obesity and a BMI of 25 kg/m^2 or lower was considered to indicate non-obesity.

Based on the TOAST (trial of ORG 10172 in acute stroke treatment) classification, patients with an infarct size of larger than 15 mm in diameter were considered to have a large infarct core and patients with an infarct size of less than 15 mm in diameter were considered to have a small infarct core. Based on this distinction, the patient group was divided into two subgroups, as patients with a large or a small infarct core. Conscious patients were informed about the aim of the study and their oral consent to participate was obtained, whereas consent in relation to unconscious patients was requested from their guardians.

The exclusion criteria were as follows: resolution of neurological symptoms within the first 24 h; hemorrhagic CVD diagnosed through clinical and neuroradiological examinations; a history of ischemic stroke; presence of cardiac

diseases that could cause cardioembolism, such as atrial fibrillation, advanced-stage heart failure or cardiac valvular disease; obesity secondary to Cushing's syndrome or to a congenital syndrome; central nervous system (CNS) vasculitis; congenital vascular diseases; trauma; cerebral venous sinus thrombosis (CVST); thyroid or kidney dysfunction; hepatic failure; local and systemic infections; or a history of dissection.

Serum chemerin concentrations were measured within the first 48 h after hospitalization. A total of 5 mL of venous blood was collected from each subject. After a 30-min coagulation period, the specimens were centrifuged at 5,000 rpm for 3 min and then serum was separated. The specimens were placed in Eppendorf tubes and stored at -20°C until analysis. The same procedure was performed in the control group. Chemerin levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Aviscera Bioscience, 2348 Walsh Ave. Suite C, Santa Clara, CA 95051, USA). The specimens were diluted to 1/40 and the results were expressed as ng/mL.

Statistical analysis

The data were analyzed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed as mean±standard deviation (SD). Continuous variables were compared using Student's t-test and the categorical variables were compared using the chi-square test. Normal distribution of data was assessed using the Kolmogorov-Smirnov test. For parameters showing non-normal distribution, data sets (chemerin levels) were transformed into natural logarithms prior to statistical analysis. Correlations were determined using the Pearson product-moment correlation coefficient (PPMCC). P<0.05 was considered significant.

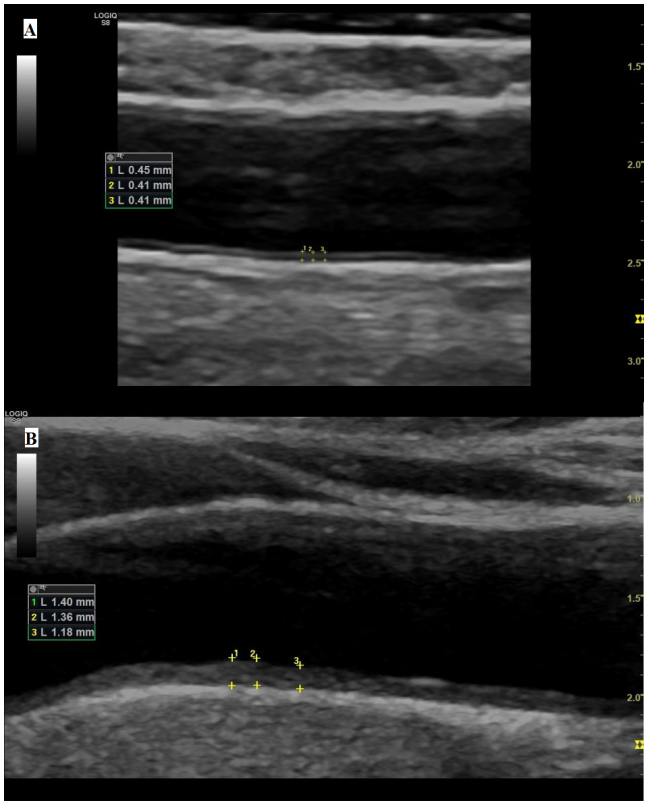

Figure 1. (A) CIMT within normal limits (<1 mm); (B) increased CIMT (1>mm).

RESULTS

The study included a total of 80 subjects, comprising 40 patients and 40 healthy individuals. The patient group included 21 women (52.5%), and the mean age of this group was 62.70±4.15 years. The control group included 29 women (72.5%), and the mean age of this group was 60.38±6.99 years (Table 1). No significant difference was found between the two groups with regard to age or gender (p=0.105 and p=0.075, respectively).

Table 1 presents the mean levels of serum parameters in the two groups. The mean chemerin level was significantly higher in the patient group than in the control group (p=0.004). Similarly, the mean LDL and triglyceride levels were significantly higher in the patient group than in the control group (p=0.006 and p<0.001, respectively). However, although the FBG levels were higher in the patient group than in the control group, no significant difference was found (p=0.130). Both SBP and DBP measurements were significantly higher in the patient group than in the control group (p<0.001). Mean BMI was significantly higher in the patient group than in the control group, which indicated that there was a significant difference between the two groups with regard to obesity (p<0.001). Mean CIMT was 1±0.2 mm in the patient group, but 0.6±0.1 mm in the control group, and this difference was significant (p<0.001).

Table 2 presents a comparison of clinical and demographic characteristics based on infarct size. Although the mean chemerin level was higher in the patients with a large infarct core (1068.3±800.96 ng/mL) than in the

Table 1. Demographic and clinical parameters.

	Patients (n=40)	Controls (n=40)	p-value
Age	62.70±4.15	60.38±6.99	0.075
Gender (F/M)	21/19	29/11	0.105
Chemerin (ng/mL)	967.11±779.39	575.42±274.54	0.004
Triglyceride (mg/dL)	162.95±131.57	102.22±37.90	0.006
LDL (mg/dL)	132.42±34.53	96.85±20.13	<0.001
FBG (mg/dL)	115.70±38.80	104.00±28.86	0.130
SBP (mmHg)	141.75±19.70	125.38±16.38	<0.001
DBP (mmHg)	88.12±13.71	73.62±13.82	<0.001
CIMT (mm)	1.01±0.22	0.64±0.13	<0.001
BMI (kg/m^2)	27.98±2.07	25.39±1.41	<0.001

LDL: low-density lipoprotein, FBG: fasting blood glucose, SBP: systolic blood pressure, DBP: diastolic blood pressure, CIMT: carotid intima-media thickness, BMI: body mass index.

patients with a small infarct core (855.85±760.50 ng/mL), this difference was not significant (p>0.05). Similarly, no significant differences were found between the two groups with regard to CIMT, age and BMI, LDL, triglyceride, FBG, SBP and DBP levels.

In the patient group, serum chemerin level showed a strong correlation with CIMT (p<0.001; r=0.786) (Table 3). However, no significant correlations were found between serum chemerin level and age, BMI, SBP, DBP, FBG, LDL and triglyceride level (p>0.05 for all). Moreover, CIMT showed a moderate positive correlation with serum chemerin level (p=0.005; r=0.432); weak correlations with age, SBP, LDL and BMI; and no correlations with FBG, triglyceride level and DBP (Table 4).

In the control group, serum chemerin level showed a moderate correlation with CIMT; weak correlations with age, BMI, LDL, SBP and DBP; and no correlations with FBG and triglyceride level. On the other hand, CIMT showed moderate correlations with age, BMI and triglyceride; weak correlations with LDL and DBP; and no correlations with FBG and SBP.

Table 2. Comparison of clinical and demographic characteristics based on infarct size

	Small (n=21)	Large (n=19)	p-value
Age	63.57±4.04	61.84±3.81	0.166
BMI (kg/m^2)	28.05±2.11	27.89±2.08	0.819
Chemerin (ng/mL)	1068.3±800.96	855.85±760.50	0.397
Log. chemerin	2.93±0.25	2.84±0.19	0.284
Triglyceride (mg/dL)	143±133.51	185±129.31	0.320
LDL (mg/dL)	128.19±32.35	137.11±37.11	0.422
FBG (mg/dL)	108.90±23.04	123.21±50.58	0.249
SBP (mmHg)	143.33±18.86	140.00±20.95	0.599
DBP (mmHg)	89.52±14.31	86.58±13.23	0.505
CIMT (mm)	1.01±0.25	1.00±0.19	0.893

BMI: body mass index, LDL: low-density lipoprotein, FBG: fasting blood glucose, SBP: systolic blood pressure, DBP: diastolic blood pressure, CIMT: carotid intima-media thickness.

Table 3. Relationship between carotid intima-media thickness and chemerin and other parameters in the patient group

Correlation	n	Pearson (r)	p-value
Chemerin* CIMT	40	0.786**	<0.001
Chemerin* age	40	0.231	0.151
Chemerin* BMI	40	0.306	0.054
Chemerin* SBP	40	0.190	0.239
Chemerin* DBP	40	0.189	0.242
Chemerin* FBG	40	0.136	0.402
Chemerin* LDL	40	0.227	0.159
Chemerin* triglyceride	40	0.112	0.491

CIMT: carotid intima-media thickness, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, LDL: low-density lipoprotein; *: relationship between parameters; **significant relationship.

DISCUSSION

The present study investigated the relationship between serum chemerin level and CIMT and found a strong correlation between serum chemerin level and CIMT in the patient group (r=0.786) and a moderate correlation in the control group (r=0.432). Moreover, mean serum chemerin level was significantly higher in the patients with ischemic stroke than in the healthy controls (p=0.04). However, no significant difference was found between the patients with large and small infarct cores with regard to serum chemerin levels (p=0.397). Additionally, mean CIMT was 1±0.2 mm in the patient group, but 0.6±0.1 mm in the control group, and this difference was significant (p<0.001).

Ischemic stroke is a leading cause of death worldwide[19]. Acute ischemic strokes are mainly of atherosclerotic origin[2]. Atherosclerosis is a progressive inflammatory disease characterized by the formation of atherosclerotic plaques caused by the presence of progressive infiltration and accumulation of lipids, smooth muscle cells and extracellular matrix in the arterial wall. Inflammation has been shown to have a key role in the formation, enlargement and destabilization of atheromas[20]. The inflammatory process begins with impairment of vascular homeostasis, caused by stimulation of the arterial wall through repeated metabolic stimulants associated with factors including hypertension, insulin resistance and obesity. This, in turn, leads to a number of conditions, including recruitment of inflammatory cells, elevated levels of adhesion molecules, increased expression of chemoreactants and proinflammatory cells from endothelial cells and migration and proliferation of medial smooth muscle cells[21].

Evidence suggesting that adipose tissue not only is a passive fuel reservoir but also an endocrine organ is accumulating. Adipose tissue secretes adipokines that act locally and distally due to their autocrine, paracrine and endocrine effects[22]. Chemerin is one of the multiple adipokines secreted by adipose tissue. Chemerin acts as a ligand

Table 4. Correlation between carotid intima-media thickness and chemerin and other parameters in the control group.

Correlation	n	Pearson (r)	p-value
Chemerin* CIMT	40	0.432	0.005
Chemerin* age	40	0.359	0.023
Chemerin* BMI	40	0.336	0.034
Chemerin* SBP	40	0.346	0.029
Chemerin* DBP	40	0.257	0.109
Chemerin* FBG	40	-0.040	0.808
Chemerin* LDL	40	0.324	0.041
Chemerin* triglyceride	40	0.094	0.563

CIMT: carotid intima-media thickness; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; LDL: low-density lipoprotein; *: relationship between parameters.

for CMKLR1 (also known as Chem R23 or 21 DEZ), which is a G protein-coupled receptor (GPCR)[23,24]. Chemerin is expressed not only in adipose tissue but also in multiple other tissues, including the liver, kidneys, pancreas, lungs, ovaries and pituitary gland. CMKLR1, on the other hand, is expressed on various immune cells such as neutrophils, active macrophages and dendritic cells[7]. Chemerin acts as a chemoreactant that recruits immune cells towards the damage site[7,25].

In a previous study, a strong correlation between plasma chemerin levels and blood pressure was found in patients with normal glucose tolerance, and it was suggested that chemerin may have a role in the regulation of blood pressure[26]. In another study, a relationship between serum chemerin levels and BMI, serum triglyceride level and blood pressure was found, and it was suggested that chemerin promotes adipocyte differentiation and plays a role in inflammation[27]. In the present study, as shown in Table 3, a strong correlation was found between serum chemerin level and CIMT in the patient group (r=0.786), while no significant correlations were found between serum chemerin level and age, BMI, SBP, DBP, FBG, LDL, and triglyceride level. As seen in Table 4, a moderate correlation was found between serum chemerin level and CIMT (r=0.432) and weak correlations were found between serum chemerin level and age, BMI, SBP and LDL (r<0.400). However, no correlations were found between serum chemerin level and DBP, FBG and triglyceride level (p>0.05). Taken together, these findings imply that serum chemerin level is an independent risk factor for plaque instability and may lead to atherosclerosis at the damage site during the inflammatory process.

Kaur et al.[25] showed that the G protein-coupled receptor CMKLR1 was present in human endothelial cells and that it was markedly upregulated by proinflammatory cytokines (TNF-a, IL-1 and IL-6). These findings imply that expression of chemerin and its receptors during the inflammatory process may lead to impaired angiogenesis and cardiovascular diseases. Hart and Graves[28] advocated that chemerin can contribute to the development of atherosclerosis through stimulating macrophage adhesion to extracellular matrix proteins, fibronectin and vascular cell adhesion molecule 1 (VCAM1). In contrast, Becker et al.[29] showed that expression of chemerin had no effect on the development of atherosclerotic lesions in LDL receptor knockout mice. These authors concluded that chemerin may contribute to the formation and morphology of atherosclerotic plaques rather than to the development of atherosclerotic lesions. In another study, aortic and coronary atherosclerosis was evaluated in 41 autopsy cases and a positive correlation was found between chemerin expression and periaortic and epicardial adipose tissue, thus confirming the paracrine effect of chemerin on atherosclerosis[30].

Cao et al.[31] investigated whether elevated C-reactive protein (CRP) is a risk factor for ischemic stroke, independent of CIMT, and evaluated the relationship between CRP and CIMT. Their study had a follow-up of over 10 years and they concluded that elevated CRP was a significant risk factor for ischemic stroke. O'Leary et al.[32] investigated the relationship between CIMT and the incidence of new myocardial infarction or stroke and found a positive correlation between CIMT and cardiovascular risk factors. Similarly, Yoo et al.[33] found significant positive correlations between serum chemerin level and BMI (p<0.00), LDL-cholesterol (p=0.042), triglyceride (p<0.00) and CRP (p=0.004) and found a weak correlation between serum chemerin level and CIMT (r=0.065; p=0.504). On the other hand, Zhao et al.[34] compared serum chemerin levels and cerebrovascular parameters between patients with acute ischemic stroke and healthy subjects in a Chinese population and reported that serum chemerin level may be an independent risk factor for acute ischemic stroke and carotid artery plaque instability.

In our study, no significant relationship was found between the patients with large and small infarct cores with regard to serum chemerin levels and CIMT (p>0.05). Similarly, Delikan et al.[35] reported that the mean CIMT was higher in patients with a large infarct core than in patients with a small infarct core, although that difference was not significant. Given that large and small infarct cores share the same etiopathogenesis in ischemic cerebrovascular disease, these findings suggest that the size of ischemic infarcts has no effect on serum chemerin concentration.

Some of the limitations of this study include the small sample size, which prevented a more detailed statistical analysis. Moreover, the potential relationship between serum chemerin level and the National Institutes of Health Stroke Scale (NIHSS) score at hospital admission or discharge was not analyzed. Furthermore, several pitfalls and problems may be encountered in ultrasound examinations on carotid arteries. Lack of a "double-line" sign can be overcome through repeated attempts to obtain horizontal positioning of the vessel on the screen, by moving the transducer perpendicular to the vessel and adjusting focus and gain. In cases of excessive vessel tortuosity, further extension and slightly neck rotation elongate the vessel segment. If the translation artifact from a pulsatile jugular vein appears in the screen, the patient can be asked to hold his breath at mid-inspiration, to stabilize the image. This is one of the most important methodological issues relating to correctly assessing CIMT.

In conclusion, the results indicated that serum chemerin level can be a predictive factor for the development of atherosclerotic ischemic cerebrovascular disease, which is a significant cause of morbidity and mortality. Further large-scale studies are needed in order to substantiate our findings.

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