Original Article

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Relationship Between Plasma Chemerin Levels and Supraventricular Tachycardia

Plazma Chemerin Seviyeleri ile Supraventriküler Taşikardi Arasındaki İlişki

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ABSTRACT

Objective: Epicardial adipose tissue is the local energy source for the contraction activity of the heart. However, chemerin is a novel chemoattractant adipocytokine released from adipose tissue. Chemerin and its receptor have been detected in epicardial adipose tissue and cardiomyocytes. The relationship between chemerin and cardiovascular diseases such as hypertension, diabetes, obesity, dyslipidemia, coronary heart disease, and atrial fibrillation has been demonstrated in previous studies. As the causes of supraventricular tachycardia (SVT), which is one of the many types of arrhythmias, are still clearly unknown, SVT is still an important source of life-threatening morbidity. In the present study, the purpose was to determine possible relations between plasma chemerin level, which had relation with cardiovascular diseases, with SVT.

Methods: A total of 62 patients, who were diagnosed as having SVT by the cardiology clinic, and 27 controls were included in this study. Hematological and serum biochemistry parameters were analyzed. The plasma chemerin concentrations were measured with the ELISA technique.

Results: Chemerin levels were higher at statistically significant levels in SVT group compared to the control group ($p<0.001$). The heart rate per minute was significantly lower in the control group compared to the patient group ($p<0.001$). The Pearson's correlation analysis revealed that there was a positive correlation between chemerin levels in plasma and average heart rate. Also, neutrophil/lymphocyte ratio was significantly higher in SVT group than in the control group (1.95±26.53 vs. 1.42±0.7, $p<0.01$).

ÖZ

Amaç: Epikardiyal yağ dokusu, kalbin kasılma aktivitesi için lokal enerji kaynağıdır. Bununla birlikte, chemerin, yağ dokusundan salınan yeni bir kemoatraktan adipositokindir. Chemerin ve reseptörü epikardiyal yağ dokusunda ve kardiyomiyositlerde tespit edilmiştir. Hipertansiyon, diyabet, obezite, dislipidemi, koroner kalp hastalığı ve atriyal fibrilasyon gibi kardiyovasküler hastalıklar ile chemerin arasındaki ilişki önceki çalışmalarda gösterilmiştir. Birçok aritmi tipinden biri olan supraventriküler taşikardinin (SVT) nedenleri hala net olarak bilinmediğinden, SVT hala hayatı tehdit eden önemli bir morbidite kaynağıdır. Bu çalışmada kardiyovasküler hastalıklarla ilişkisi olan plazma chemerin düzeylerinin SVT ile olası ilişkilerinin belirlenmesi amaçlanmıştır.

Yöntemler: Bu çalışmaya kardiyoloji kliniği tarafından SVT tanısı konulan toplam 62 hasta ve 27 kontrol dahil edildi. Hematolojik ve serum biyokimya parametreleri analiz edildi. Plazma chemerin konsantrasyonları ELISA tekniği ile ölçüldü.

Bulgular: Chemerin düzeyleri kontrol grubuna göre SVT grubunda istatistiksel olarak anlamlı düzeylerde daha yüksekti ($p<0,001$). Dakikadaki kalp hızı, kontrol grubunda hasta grubuna göre anlamlı derecede düşüktü ($p<0,001$). Pearson korelasyon analizi, plazmadaki chemerin seviyeleri ile ortalama kalp hızı arasında pozitif korelasyon olduğunu ortaya koydu. Ayrıca nötrofil/lenfosit oranı SVT grubunda kontrol grubuna göre anlamlı derecede yüksekti (1,95±26,53 vs. 1,42±0,7, $p<0,01$).

Sonuç: Bu çalışma ilk kez SVT'de plazma chemerin düzeylerinin yüksek olduğunu gösterdi. Ayrıca bu çalışma yüksek plazma

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ABSTRACT

Conclusion: This study showed for the first time that plasma chemerin level was elevated in SVT. In addition, this study determined a positive correlation between high plasma chemerin concentration and heart rate. Determining and controlling the circulating level of chemerin, which is associated with cardiovascular diseases, inflammation, metabolic syndrome and many other diseases, may be important in SVT.

Keywords: Supraventricular tachycardia, chemerin, arrhythmia, cardiovascular diseases

ÖZ

chemerin konsantrasyonları ile kalp atım hızı arasında pozitif bir korelasyon olduğunu belirledi. Kardiyovasküler hastalıklar, enflamasyon, metabolik sendrom ve daha birçok hastalıkla ilişkisi bulunan chemerinin dolaşımdaki seviyelerini belirlemek ve düzeylerini kontrol etmek SVT'de önemli olabilir.

Anahtar Sözcükler: Supraventriküler taşikardi, chemerin, aritmi, kardiyovasküler hastalıklar

Introduction

Supraventricular tachycardia (SVT) is a general term that is used for all tachycardias that originate from above the atrioventricular node. Arrhythmias, such as atrioventricular nodal reentrant tachycardias (AVNRT), atrioventricular reentrant tachycardias (AVRT), which are caused by various accessory pathway-mediated mechanisms, Atrial Tachycardia, and sinus tachycardias, which are caused by single and multi-focal mechanisms, and atrial flutter and atrial fibrillation are also included in Supraventricular Tachycardias. Paroxysmal SVT is the term used for the subset of SVT, including AVNRT, AVRT, and AT, which have a sudden onset (1).

The anatomical basis of the pathophysiology of SVT (AVRT, AVNRT) is still not known, and the specific abnormalities of the special transmission system have still not been elucidated. However, it should be considered that some types, such as atrial fibrillation and atrial flutter, have more complex pathological backgrounds (2). Many hypotheses have been speculated to explain the etiology of SVT, including the possibility that inflammatory condition triggers arrhythmia (3). It has been foreseen in limited studies that systemic inflammation markers, such as total leukocyte count and subtypes, e.g. neutrophil, lymphocyte, and neutrophil/lymphocyte ratio (NLR), can be used to diagnose SVT (4).

The epicardial fat, which appears as a result of the accumulation of the visceral fat around the heart, plays roles in atrial arrhythmogenesis with its ability to produce and excrete a large number of adipocytokines as an ectopic fat storage with endocrine and inflammatory features near the atrium (5). The plasma level of chemerin, which is an adipocytokine excreted by the epicardial adipose tissue, is elevated in atrial fibrillation. However, chemerin also regulates inflammatory response by affecting the calcium homeostasis, connexins, and atrial electrophysiology in cardiac tissue (6).

Although there are very few studies showing relation between SVT and NLR, there are no studies showing relation between plasma chemerin levels and SVT. The purpose of this study was to search for relation between chemerin levels in the circulation of patients with SVT and possible arrhythmogenic effects of chemerin, and to suggest a useful marker that could be used in the diagnosis and that could be added to clinical parameters.

Methods

Patient Population

A total of 62 patients, who were diagnosed as having SVT and admitted to the Cardiology Clinic of Afyonkarahisar Health Sciences University, Faculty of Medicine between November 2019 and November 2020, were included in our study. These participants were matched in terms of age, gender, and ethnicity with 27 healthy adults who had no palpitation symptoms and arrhythmic disease, and who had normal physical examination results, and who were admitted to the adult cardiology clinic for examinations. G*Power 3.1.9.7 was used to calculate the minimum number of participants required to observe a significant difference between two groups at $p<0.05$ (two-tailed test). To obtain a statistical power of 80 for a medium effect size (Cohen's d=.65) a total of 90 participants were required. Individuals with narrow QRS tachycardia documented by electrocardiography and SVT documented electrophysiologically were included in the SVT group. All patients with SVT included in the study had AVRT, AVNRT or AVRT. However, since atrial fibrillation and atrial flutter had different clinical evaluations, they were not included in our study.

Oral and written informed consent forms were received from all patients and healthy volunteers who participated in the study after receiving the approval of the ethics committee for the study (2019/350). Patients with coronary artery disease, heart failure, suspected myocarditis, pericarditis, unstable angina pectoris, ST segment depression due to myocardial infarction, impaired kidney functions (i.e. creatinine levels >1.4 mg/dL), autoimmune disease, acute or chronic hepatic or hepatobiliary disease, pulmonary hypertension, or any malignant history were excluded from the study. Standard 12-lead ECGs were performed for all subjects during the registration.

Blood Sampling and Laboratory Methods

Blood samples were collected after 12 hours of fasting after admission to the hospital. Five mL venous blood samples were taken from all individuals, centrifuged for 15 minutes at 1,000 rpm in cooled centrifuge device, plasmas were separated, and were then stored at -70 ºC until the analyses were performed. Total and differential leukocyte counts and routine biochemical and hematological tests were performed in line with the

procedures. Furthermore, the distributions of hemogram and full biochemistry parameters in all patients and controls were examined.

Measurement of Plasma Chemerin Levels

Plasma chemerin level was examined with a commercially available enzyme immunoassay kit (Bioassay Technology Laboratory, Shanghai, China) in line with the instructions of the manufacturer. The absorbance reading of the samples was carried out with the Chromate 4,300 brand ELISA Reader Device (Awareness Technology, Inc. Martin Hwy, Palm City, USA). The mean values that were obtained with duplicated tests on the samples were given as ng/L.

Statistical Analysis

Categorical variables were presented as numbers and percentages, and were compared with the chi-square test. Continuous variables were expressed as mean and SD. The intergroup continuous variables that had normal distribution were compared by using the Independent Samples T-test, or those that did not show normal distribution were compared with the Mann-Whitney U test. The Pearson chi-square analysis was made to evaluate the independent predictors of SVT. Statistical analyses were made with the Statistics Program for Social Sciences (SPSS 15.0. Inc. Chicago, Illinois, USA), and $p<0.05$ was considered as statistically significant.

Results

The main characteristics of the patients included in the study are summarized in Table 1. No significant difference was detected between the patient group and the control group in terms of gender, age and major risk factors (i.e. hypertension, diabetes mellitus, cerebrovascular accident, dyslipidemia, smoking history). Also, no statistically significant difference was detected in terms of body mass index (BMI), body surface area, and systolic blood pressure measurements aside from hematological and biochemical measurements such as lymphocyte, leukocyte and platelet counts, and blood urea nitrogen, glucose, triglyceride, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), potassium, sodium, chlorine, thyroid stimulating hormone, T3, and T4 levels ($p>0.05$). However, statistically low-level and significant differences were detected in terms of calcium levels in the patient group compared to the control group ($p<0.01$). There was a statistically significant difference in terms of chemerin level in the SVT group compared to the control (SVT group; 485±143.40 and control group; 293±22.85, $p<0.001$) (Table 1, Figure 1). Heart rate per minute was significantly higher in the SVT group than in the control group ($p<0.001$); and a positive correlation was detected between chemerin level in plasma and average heart rate. Figure 2 shows a positive correlation between chemerin level and heart rate in all patients participating in the study ($r=0.279$, $p<0.01$). Although the neutrophil count was significantly higher in the SVT group than in the controls (4.41±2.01, 3.74±1.26, $p<0.001$), lymphocyte count was lower without reaching a statistically significant level in the SVT group than in the control group (2.42±0.93, 2.44±0.81, $p>0.05$). As a result, the NLR, which was one of the independent predictors of SVT, was higher in the SVT group compared to the control group (1.95±26.53, 1.42±0.7, $p<0.01$). However, although platelet lymphocyte ratio (PLR) and C-reactive protein (CRP) level, which were among the other inflammation markers, were higher in the patient group, this was not statistically significant (Table 2).

Discussion

Epicardial adipose tissue is an ectopic fat storage near the atrium, and can play roles in cardiac pathophysiology with its endocrine and inflammatory features (5). Adipocytokines that are released from this area can have paracrine effects and affect myocardial functions and the incidence of atrial and ventricular arrhythmias due to the proximity of epicardial fat to neuronal plexus and cardiomyocytes (7). The coronary perivascular adipose tissue, which is a part of the epicardial adipose tissue, is defined as the adipose tissue that surrounds the coronary arteries or the perivascular adipose tissue (PAT) (8). Chemerin is mostly produced in the visceral adipose tissue, liver, lungs, heart, ovaries, kidneys, pancreas, and in the placenta albeit in lower amounts (9-12).

Recent studies show that elevated chemerin concentration in the serum is positively correlated with obesity, dyslipidemia, insulin resistance, hypertension, diabetes, coronary artery disease, and renal failure (13). Elevated chemerin level in the circulation is also positively associated with various factors of the metabolic syndrome, such as high glucose level in the circulation, high triglyceride level, low HDL level, high LDL level, and BMI (10,14-16). When considered with a clinical viewpoint, chemerin level in the circulation also has positive correlations with inflammation markers such as CRP. The risk of development of metabolic syndrome and also cardiovascular diseases is increased in obese patients as they have ten-fold more chemerin in their circulation when compared with healthy individuals (17).

SVT is a common and rapid arrhythmia type in patients who do not have organic heart disease, and is caused by electrical stimuli originating from above the ventricles of the heart (18). In line with the Coumel Theory, three elements are needed for clinical arrhythmia development. These three elements are an anatomically-evolving ectopic accessory pathway, a triggering factor, and a modulator caused mostly by the autonomous nervous system (19). Although triggering factors are still a matter of debate, and although it may often be an extrasystole pulse, it is still unclear what causes SVT (20).

Heart rhythms stem from the electrical activity generated by the opening-closing of the ion channels in cardiomyocytes. The opening of the voltage-gate sodium channel initiates the spread of an electrical action potential promoting the cellular depolarization and coordinated contraction of the heart. The change in the function of the ion channel is associated with a wide range of cardiac transmission pathologies such as arrhythmias (21). Voltage-gate sodium channels are expressed at high rates in all types of cardiac myocytes, in sinus node, transmission pathways,

and in atrial and ventricular myocytes (22). The ion distributions of the sodium, potassium, and calcium ions inside-outside the cell, which contribute primarily to membrane potential, change the membrane potential. For this reason, abnormalities that occur in the formation of the action potential not only affect the contraction power of the heart, but also the rate at which the heart beats per minute (23). Yamamoto et al. (24) conducted a study and showed that acute intra-cerebral chemerin-9 injection increased systemic blood pressure, and also that the treatment of chemerin CMKLR1 receptor with siRNA eliminated this effect. In their study, although they were unable to identify a specific nucleus and/or cells that were associated with the elevation of the blood pressure, they speculated that chemerin might cause projection in the cardiovascular center with voltage-gate sodium channels and peripheral sympathetic nervous system activation. The endogenous chemerin coming from the PAT such as leptin adipocytokine strengthens the effects of the sympathetic nerve function (25). However, current studies showing that chemerin

Table 1. Basic demographic, hematological, and biochemical characteristics of the study population

Variable	Patient		Control		
	Mean/median	SD	Mean/median	SD	P
Female, n (%)	35 F (56.5%) 27 M (43.5%)		13 F (48.1%) 14 M (51.9%)		0.4**
Age (year)	56.38	14.64	57.64	10.23	0.69
Body mass index, kg/m^2	28.90	4.81	29.47	6.69	0.6
Body surface area	1.94	3.4	1.88	0.1	0.08*
Systolic BP, mm/Hg	131.5	11.86	128.46	10.26	0.2
Diastolic BP, mm/Hg	79.20	13.33	72.79	10.25	**0.01**
Heart rate	84.31	11.96	74.07	9.99	**0.000**
Neutrophil count (10^3/µL)	4.41	2.01	3.74	1.26	**0.001***
Lymphocyte count (10^3/µL)	2.42	0.93	2.44	0.81	0.95
Leukocyte count (10^3/µL)	8.16	2.27	7.77	2.14	0.44
Platelet count (10^3/µL)	278.17	84.57	254.51	73.31	0.21
BUN (mg/dL)	15.23	8.17	12.85	6	0.29*
Fasting glucose (mg/dL)	98.50	23.09	103	47.82	0.12*
Total cholesterol (mg/dL)	172.8	41.76	177.70	38.62	0.61
HDL (mg/dL)	46.00	40.02	39.35	11.67	0.4
LDL (mg/dL)	112.92	35.26	109.09	36.09	0.6
Potassium, level	4.54	0.4	4.63	0.3	0.31
Calcium, level	9.21	0.64	9.58	0.55	0.01
Sodium level	139.80	3.1	135.11	24.75	0.33
Chlorine level	102.66	3.67	101.59	2.74	0.18
TSH (mIU/L)	1.47	1.19	1.42	0.95	0.7*
T3 (mIU/L)	2.87	0.63	2.95	0.49	0.52
T4 (mIU/L)	1.29	0.25	1.35	0.2	0.23
Chemerin ng/L	485	143.40	293	22.85	0.000
Hypertension, n (%)	31 (50%)		13 (48.1%)		0.8
Diabetes, n (%)	9 (14.5%)		9 (33.3%)		0.06**
SVO, n (%)	2 (3.2%)		-		0.34**
Dyslipidemia, n (%)	5 (8.1%)		2 (7.4%)		0.9**
Beta blocker, n (%)	38 (61.3%)		10 (37%)		**0.03****
ACEI treatment, n (%)	25 (40.3%)		8 (29.6%)		0.3**
Smoking, n (%)	24 (38.7%)		11 (40.7%)		0.8**

*Mann-Whitney U test, **Chi-square (x^2) test, Independent Samples t-test were used for other parameters.
SD: Standard deviation, BP: Blood pressure, HDL: High density lipoprotein, LDL: Low density lipoprotein, TSH: Thyroid stimulating hormone, SVO: Cerebrovascular event

induces L-type calcium channel activation, (26) and that L-type calcium channel reduces mRNA expression level (27) also show that chemerin can participate in intracellular ion regulation after modifying the function and structure of calcium channels. It was found in our study that calcium level was lower in the SVT group than in the control group. Extracellular low ionized calcium level increases the ion channel's permeability to sodium ion, causing progressive depolarization and increases the probability of action potential as a result of calcium ions' interaction with the outer surface of sodium channels in the plasma membrane of the nerve cells. It increases the potential for resting effectively, in other words, make cells more prone to be stimulated (28).

In a study conducted with patients who had atrial fibrillation, increased chemerin level was detected in circulation. It was determined in the same study that patients with permanent atrial fibrillation had higher chemerin level when compared to patients with persistent and paroxysmal atrial fibrillation (29). There are no studies supporting that chemerin affects heart rate directly. However, another study reporting that heart rate decreased unexpectedly in rats of which chemerin gene was knocked-out supported that there might be an interaction between chemerin level and heart rate (30). Based on the literature data mentioned so far, it can be argued that chemerin can affect the electrophysiology of the heart including myocytes in the sinoatrial node through sympathetic nervous system activation and ion channels, such as sodium, calcium by shortening the duration of action potentials.

It was foreseen with this study for the first time in the literature that chemerin, which was elevated in circulation of the patients with SVT, might contribute to the physiopathology of SVT, or might be used as a predictor. A positive correlation was detected between the elevated heart rate and plasma chemerin level in patients with SVT. Our study is original in this context in terms of its contribution to the literature.

The NLR, PLR, and CRP level, which were the independent predictors of SVT, and possible effect of chemerin on these values constituted another point that was investigated in our study. The number of the leukocyte subtypes and the NLR were among systemic inflammation indicators (31,32), and the important role of NLR in inflammation was discussed in previous studies conducted on SVT (33,34). CRP, which is one of the other markers of inflammation, is an important descriptive marker in patients with atrial tachycardia. Although the causal relation between CRP and atrial tachycardias is not fully elucidated, it can be concluded that inflammation will be associated with atrial tachycardias (4). Premature atrial and ventricular contractions are the most common triggering factors for SVTs. There is a strong relation between premature ventricular contractions and NLR. Other myocardial conditions and this inflammatory condition, which results in early contractions, have also roles in initiating SVTs (35-37). Based on these data, it can be speculated that the NLR, which will indicate a possible inflammatory condition, can also induce SVT (4). Also, the effects of anti-inflammatory axis of chemerin and its receptor CMKLR1 have also been reported in this respect. It is considered that chemerin inhibits neutrophil and monocyte aggregation in the peritonitis model, reduces proinflammatory mediators, and regulates the inflammatory process during which the presence of neutrophils may increase plasma chemerin levels by inducing the formation of chemerin homologues (38).

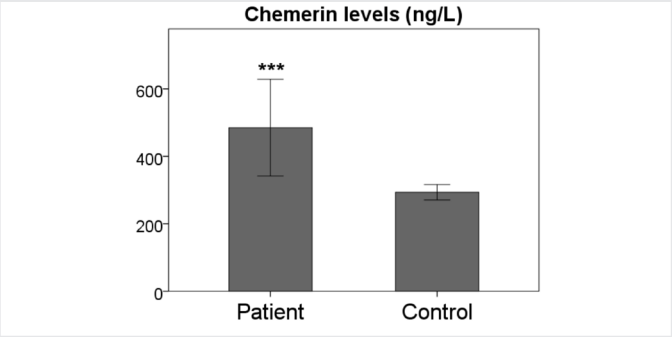

Figure 1. Difference in chemerin levels between the patient (SVT) group and control group (***p<0.001)

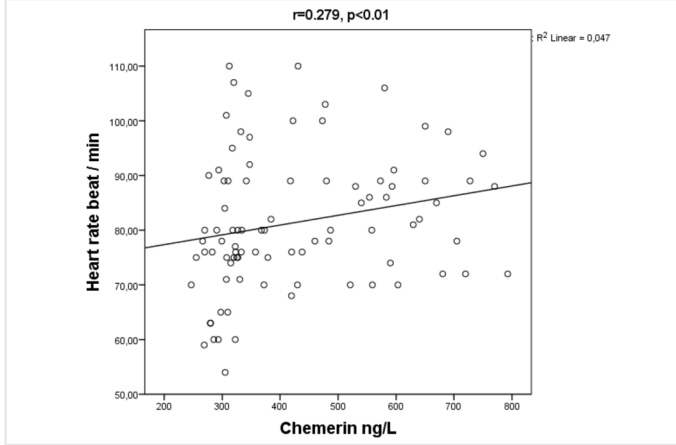

Figure 2. Correlation between chemerin and heart rate in the entire study group

Table 2. Independent predictors of supraventricular tachycardia

Variable	Patient		Control		
	Median	SD	Median	SD	P
*NLR	1.95	26.53	1.42	0.7	**0.01**
*PLR	122.09	1007.96	107.09	30.49	0.1
*C-reactive protein	0.45	1.23	0.3	1.34	0.27

NLR: Neutrophil/lymphocyte ratio, PLR: Platelet lymphocyte ratio, SD: Standard deviation

Study Limitations

The date of this study coincided with the coronavirus disease-19 pandemic, making it difficult to reach the number of patients required for the study. This study also demonstrated for the first time that there might be an association between SVT and chemerin, an endogenous adipocytokine. However, a cause-effect relationship could not be established in the relationship between chemerin and SVT, and a causality assessment could not be made.

Conclusion

In conclusion, for the first time, the present study showed the relation between plasma chemerin level and SVT, and the positive relation between high chemerin concentration and heart rate was also revealed. Also, similar to previous studies, higher NLR, which was a reliable marker in inflammation, was associated with the presence of SVT. On the other hand, multicenter and wider-scale studies are required regarding the relations between inflammation, chemerin, and SVT trio in the pathogenesis process, which may be triggered by chemerin through ion gates, contributing to the organization of inflammation, which, then, may play roles in the formation mechanism of SVT, and this inflammatory process in the body.

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Ethics

Ethics Committee Approval: All procedures were performed after the study was approved by Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (2019/350).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.Y., Concept: Ö.K., Design: Ö.K., Data Collection or Processing: Ö.K., Z.Y., Analysis or Interpretation: Ö.K., Z.Y., Literature Search: Ö.K., Writing: Ö.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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