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Evaluation of Serum Resistin Levels and Metabolic Syndrome Related Parameters in Chronic Spontaneous Urticaria

Kronik Spontan Ürtikerde Serum Resistin Düzeyi ve Metabolik Sendrom İlişkili Parametrelerin Değerlendirilmesi

Abstract

Objective: To evaluate the relationship between the serum resistin levels and metabolic syndrome (MetS) in chronic spontaneous urticaria (CSU) patients.
Methods: In the study 42 CSU patients and 42 healthy volunteers were included. Height, weight, waist circumference, and blood pressure measurements were assesed for both of the groups. Fasting blood sugar, serum lipid levels, resistin and tumor necrosis factor-alpha (TNF-a) levels were evaluated in the venous blood samples. The metabolic syndrome (MetS) diagnosis was determined using the National Cholesterol Education Program Adult Treatment Panel III diagnostic criteria.
Results: MetS was found in 14 (33.3%) CSU patients and 5 (11.9%) control subjects. There was a statistically significant difference between the two groups (p=0.037) in terms of MetS presence. It was found that the mean serum resistin levels was 1928.31±212.85 pg/mL in the CSU patients and 2107.60±156.71 pg/mL in the control group. There was no statistically significant difference between the groups in terms of serum resistin levels. No difference was seen between the patients with and without a diagnosis of MetS regarding the urticaria activity score, duration of the disease, autologous serum skin test positivity, serum immunoglobulin E levels, presence of autoimmunity, serum resistin and TNF-a levels.
Conclusion: An increased incidence of MetS in the CSU patient group is found in our study. However, there was no difference between the CSU patients with and without MetS regarding the disorder-associated parameters and the serum resistin and TNF-a levels.

Keywords: Chronic spontaneous urticaria, metabolic syndrome, resistin, tumor necrosis factor-alpha, urticaria activity score, autologous serum skin test

Öz

Amaç: Kronik spontan ürtiker (KSÜ) hastalarında serum resistin düzeyi ve metabolik sendrom (MetS) ilişkisini değerlendirmek.
Yöntemler: Çalışmaya 42 KSÜ hastası ve 42 sağlıklı gönüllü dahil edildi. Boy, kilo, bel çevresi ve kan basıncı ölçümleri her iki grupta da değerlendirildi. Açlık kan şekeri, serum lipid düzeyleri, resistin ve tümör nekroz faktörü-alpha (TNF-a) düzeyleri venöz kan örneklerinde değerlendirildi. MetS tanısı National Cholesterol Education Program Adult Treatment Panell III tanı kriterleri ile belirlendi.
Bulgular: KSÜ hastalarının 14'ünde (%33,3) ve kontrol grubunun 5'inde (%11,9) MetS saptandı. İki grup arasında MetS varlığı açısından istatistiksel olarak anlamlı fark bulundu, p=0,037. KSÜ hastalarının serum resistin düzeyleri ortalaması 1928,31±212,85 pg/mL ve kontrol grubunun serum resistin düzeyleri ortalaması 2107,60±156,71 pg/mL olarak saptandı. Her iki grup arasında serum resistin düzeyi açısından istatistiksel anlamlı fark görülmedi. KSÜ hastalarında MetS tanısı olan hastalar ile MetS tanısı olmayan hastalar arasında ürtiker aktivite skoru, hastalık süresi, otolog serum deri testi pozitifliği, serum immünoglobulin E düzeyi, otoimmünite varlığı, serum resistin ve TNF-a düzeyi açısından farklılık görülmedi.
Sonuç: Çalışmamızda KSÜ hasta grubunda MetS görülme sıklığında artış olduğu saptanmıştır. Diğer taraftan KSÜ hastaları içinde MetS'yi olan ve olmayan iki grup arasında hastalık ilişkili parametreler ile serum resistin ve TNF-a düzeyi farklılık göstermemiştir.

Anahtar kelimeler: Kronik spontan ürtiker, metabolik sendrom, resistin, tümör nekroz faktörü-alfa, ürtiker aktivite skoru, otolog serum deri testi

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Introduction

Metabolic syndrome (MetS) is a combination of central obesity, dyslipidemia, glucose intolerance and elevated blood pressure (1). Increased inflammatory markers, mainly interleukin (IL) (IL-1, IL-6), tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) have been related with development of MetS in pro-inflammatory and pro-coagulation steps (2). Chronic urticaria (CU) is a skin disease characterized by recurrent urticaria lasting longer than 6 weeks. The term chronic spontaneous urticaria (CSU) is used to define CU which occurs without any known triggering factor (3). The studies demonstrated that circulating CRP, pro-inflammatory cytokines such as IL-6, TNF-α and metabolic markers are increased and procoagulation pathway is activated in CSU (4-6).

Resistin, identified firstly in 2001, is a 12.5 kDa adipokine containing 114 aminoacids (7). It is secreted from mainly adipose tissue and other tissues such as macrophages, mononuclear leukocytes, in bone marrow and spleen and induced the secretion of cytokines responsible for MetS development such as IL-6, IL-12, TNF-α (7,8). Many studies reported that resistin was associated with insulin resistance, hyperglycemia and obesity (9-11). In addition, resistin was shown to be related with inflammation and immunity in many disorders including atherosclerosis, renal disorders, respiratory system disorders and psoriasis (11,12).

Although chronic systemic inflammation is seen in patients with CSU, only one previous study investigated the relationship of MetS and CU in literature (13). In this study, we aimed to investigate serum resistin and TNF-α levels together with other metabolic parameters in patients with CSU, and we also aimed to compare urticaria-related parameters in CSU patients with or without MetS.

Material and Methods

The study included 42 CSU patients and 42 healthy volunteers. The study protocol was approved by local ethics committee. All patients and healthy volunteers gave written informed consent after they were informed about the study. Patients with complaint of urticaria or urticaria plus angioedema for at least six weeks were classified as CU. According to EAACI/GA2LEN/EDF/WAO (3) guidelines, patients without inducible urticaria etiology were accepted as CSU. Exclusion criteria were pregnancy, lactation, liver or kidney dysfunction, medication due to liver or kidney dysfunction, history of systemic inflammatory disease, systemic immunosuppressive treatment within the last 1 month and accompanying dermatologic diseases other than CSU.

Evaluation of the Presence of Metabolic Syndrome

Age, gender, height, weight, body mass index (BMI), waist circumference, and blood pressure levels of CSU patients and controls were recorded. MetS diagnosis was based on National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) (1) criteria and MetS was diagnosed in patients with 3 or more criteria [NCEP-ATP III diagnostic criteria: waist circumference in males >90 cm and in females >80 cm, triglyceride (TG) ≥150 mg/dL, high density lipoprotein (HDL) in males <40 mg/dL, in females <50 mg/dL, blood pressure >130/85 mmHg, glucose level ≥110 mg/dL].

Assessment of Urticaria Activity Score

In order to assess the disease activity in CSU patients, we used urticaria activity score (UAS). Number of wheals (0, none: 1, <10 wheals: 2, 10-50 wheals: 3, >50 wheals), and intensity of itch (0, none: 1, mild: 2, moderate: 3, severe) were assessed. Sum of daily UAS scores gave weekly UAS7 score between 0-42 points (3).

Evaluation of Autologous Serum Skin Test

Autologous serum skin test (ASST) evaluation was based on EACCI/GA2LEN/EDF/WAO guideline (3). If the wheal and flare response with autologous serum (i.e. the diameter of erythematous papule) is 1.5 mm or greater than saline, the response was positive.

Assessment of Laboratory Findings

Venous blood samples were collected from CSU patients and controls after an 8-hour fasting. Serum fasting blood glucose (FBG), TG, HDL, low-density lipoprotein (LDL) levels, high sensitivity CRP (hsCRP) were measured. In addition to these parameters, complement 3 (C3), complement 4 (C4), antinuclear antibody (ANA), thyroid stimulating hormone (TSH), anti-thyroglobulin (anti-TG), anti-microsomal antibody (anti-TPO), total IgE levels, resistin, and TNF-α levels were also evaluated in CSU patients.

Serum FBG, HDL, LDL and TG levels were all measured by using the enzymatic colorimetric method. Serum hsCRP levels was determined with the immunoturbidimetric method by using Roche/Hitachi Modular (Mannheim, Germany), C3, C4, ANA, TSH, anti-TG, anti-TPO, total IgE levels were measured by using Roche Hitachi Cobas 602 autoanalyser (Mannheim, Germany).

To assay serum resistin and TNF-α levels, venous blood samples were centrifuged and serum samples were stored at -40 °C (SANYO Freezer, Japonya) until assay. Commercial sandwich ELISA kits were used to measure serum resistin and TNF-α levels in accordance to instructions of manufacturer (resistin kit: BMS2040, eBioscience, Vienne, Austria, and TNF-α kit: BMS223/4, eBioscience, Vienne, Austria). Measurements were performed by spectrophotometry using 450 nm filter and ELISA reader (ELX-800, Biotek Instruments, United States of America). Resistin and TNF-α levels were expressed in pg/mL.

Statistical Analysis

Analysis of the data was performed by using IBM SPSS Statistics 21.0 package software. Continuous variates were expressed as mean ± standard deviation. Categoric variates were expressed as percent (%) values. Normal distribution of variables were tested by Shapiro Wilk test. Comparisons of normally distributed parameters between two groups were made by independent samples t-test. Parameters without normal distribution were compared by Mann-Whitney U test between two groups. Crosstabs were analysed by Pearson's chi-square and Pearson's exact chi-square tests. Correlation between parameters was tested by Spearman correlation test. Statistical significance level was adjusted to $p<0.05$.

Results

The study included 42 CSU patients (66.7% female, 33.3% male) and 42 healthy volunteers (66.7% female, 33.3% male). The mean age in CSU group and control group were 40.78±7.62 years and 40.00±12.26 years, respectively. There was no statistical differences patient and control group in terms of age and gender (p=0.334, p=1.00) (Table 1). BMI, waist circumference, serum TG, and hsCRP values of CSU patients were significantly higher than control group (p=0.001, p=0.01, p=0.048, p=0.031, respectively, Table 1). Serum FBG, HDL and resistin levels were not statisticaly different between the groups (p=0.380, p=0.802, p=0.057, respectively, Table 1). When serum mean TNF-α levels were compared between CSU patients and controls, serum TNF-α was significantly higher in control group than in patient group (p=0.036, Table 1). The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher in CSU patients compared to controls (p=0.013, p=0.018, Table 1). In terms of MetS presence, MetS was present in 14 (33.33%) patients of CSU group and 5 (11.90%) individuals in control group. MetS was significantly more common among CSU patients than controls (p=0.037, Table 1). Demographic and laboratory characteristics of CSU patients and controls are given in Table 1.

CSU patients were divided into two subgroups as MetS-positive and MetS-negative patients. Comparison of demographic and laboratory findings between MetS-positive and negative groups are given in Table 2. Serum resistin and TNF-α levels were similar in MetS-positive and MetS-negative CSU patients (p=0.296, p=0.788, Table 2). ASST positivity, ANA positivity, disease duration, presence of thyroid auto antibody, serum IgE, C3 and C4 levels, angioedema and atopy were not statisticaly different between MetS-positive and MetS-negative CSU groups (Table 2).

Comparison of UAS7 score between the MetS-positive and MetS-negative CSU patients revealed that UAS7 score was significantly lower in MetS-positive group than in MetS-

Table 1. Comparison of demographic and laboratory data of chronic spontaneous urticaria patients and control group

	CSU (n=42)	Control (n=42)	p
Age	40.78±7.62	40.00±12.26	0.334¶
Gender Female Male	 28 (66.7%) 14 (33.3%)	 28 (66.7%) 14 (33.3%)	1.00¶
BMI (kg/m^2)	27.95±4.23	24.79±4.31	<0.001¶
Waist circumference (cm)	88.64±11.04	81.59±13.31	0.01¶
FBG (mg/dL)	91.26±15.84	88.29±13.66	0.380¶
TG (mg/dL)	142.38±71.19	110.88±48.42	0.048¶
HDL (mg/dL)	46.90±10.14	47.68±9.87	0.802¶
LDL (mg/dL)	122.30±30.96	105.19±33.12	0.044¶
hsCRP (mg/L)	2.81±3.35	1.29±1.39	0.031¶
Resistin (pg/mL)	1928.31±212.85	2107.60±156.71	0.057¶
TNF-α (pg/mL)	59.62±73.00	63.21±42.32	0.036¶
SBP (mmHg)	120.35±14.24	113.39±11.86	0.013¶
DBP (mmHg)	77.02±10.12	113.09±14.77	0.018¶
MetS (+)	14 (33.33%)	5 (11.90%)	0.037‡

¶: Mann-Whitney U test, ‡: Pearson's chi-square test, CSU: Chronic spontaneous urticaria, FBG: Fasting blood glucose, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, hsCRP: High sensitive C reactive protein, TNF-α: Tumor necrosis factor-alpha, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MetS: Metabolic syndrome, BMI: Body mass index

Table 2. Comparison of clinical characteristics and laboratory data of patients with chronic urticaria with and without metabolic syndrome

	CSU with MetS (n=14)	CSU without MetS (n=28)	p
Age	45.00±6.62	38.67±7.30	0.01¶
Gender Female Male	 6 (42.9%) 8 (57.1%)	 8 (28.6%) 20 (71.4%)	0.490‡
BMI (kg/m^2)	31.37±8.85	26.04±6.56	0.046¶
Waist circumference (cm)	99.71±7.06	83.10±8.12	<0.001¶
FBG (mg/dL)	103.50±18.11	85.14±10.33	<0.001¶
TG (mg/dL)	188.78±55.13	119.17±67.52	<0.001¶
HDL (mg/dL)	43.35±11.05	48.67±9.36	0.110¶
LDL (mg/dL)	113.50±22.07	126.71±34.07	0.196¶
hsCRP (mg/L)	3.22±3.89	1.89±1.43	0.367¶
SBP (mmHg)	134.28±5.83	113.39±11.86	<0.001¶
DBP (mmHg)	85.00±8.08	73.03±8.64	<0.001¶
Resistin (pg/mL)	1282.15±1025.44	2167.61±2501.82	0.296¶
TNF-α (pg/mL)	59.85±4.49	59.18±8.68	0.788¶
Duration of CSU, month	27.35±4.61	26.85±3.27	0.843¶
Angioedema (%)	5 (35.70%)	18 (64.30%)	0.154‡
Atopy (%)	4 (28.60%)	7 (25.80%)	1.00‡
UAS7	19.28±8.73	26.67±9.00	0.020¶
ASST (%)	10 (7.4%)	18 (64.3%)	0.643‡
ANA (%)	1 (7.1%)	5 (17.9%)	0.645‡
Anti TG (IU/mL)	4 (28.6%)	6 (25%)	0.933‡
Anti TPO (IU/mL)	4 (28.6%)	7 (29.2%)	0.538‡
Total IgE (IU/mL)	273.45±27.90	250.68±29.80	0.321¶
C3 (mg/dL)	133.05±2.25	123.71±21.47	0.225¶
C4 (mg/dL)	30.75±8.06	27.81±6.84	0.224¶

¶: Mann-Whitney U Test, ‡: Pearson's chi-square test, CSU: Chronic spontaneous urticaria, MetS: Metabolic syndrome, BMI: Body mass index, FBG: Fasting blood glucose, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, hsCRP: High sensitive C-reactive protein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TNF-α: Tumor necrosis factor-alpha, UAS: Urticaria activity score, ASST: Autologous serum skin test, ANA: Anti nuclear antibody, Anti-TG: Anti-thyroglobulin, Anti-TPO: Anti-microsomal antibody, IgE: Immunoglobulin E, C3: Compleman 3, C4: Compleman 4

negative group (19.28±8.73 vs. 26.67±9.00, respectively; p=0.020, Table 2).

Correlation analysis showed that there was no correlation between serum resistin levels UAS7 score, serum FBG, TG, HDL, LDL, TNF-α, IgE level, and disease duration in CSU patients (Table 3).

Discussion

The role of adipokines and inflammatory cytokines including TNF-α, IL-6, IL-1β, CRP in relationship of obesity and inflammation is well known (2). It has been demonstrated that chronic systemic inflammation in dermatologic disorders such as atopic dermatitis, psoriasis, and lichen planus have an increased the risk of MetS (14-17). Although systemic inflammation has been described in CSU patients, only one study investigated the relationship of MetS and CU (13). Ye et al. (13). reported that 39 (29.8%) of 131 patients with CU had MetS. In our study, we also observed MetS in 33.3% of CSU patients. Ye et al. (13). found that diagnostic criteria of MetS, i.e. FBG, TG, and waist circumference, were significantly higher in CU group than in control group, but SBP and DBP values were comparable between the two groups. Similarly in our study, we found that waist circumference and serum TG levels were significantly higher in CSU patient group compared to controls. Unlike that study, serum FBG and HDL levels were similar in both study group of our study. In addition, the mean SBP and DBP levels were significantly higher in CSU patients than controls in this study. Besides, Chung et al. (18). reported that hyperlipidemia was significantly higher in CU patients than controls Consequently, literature data and our findings reveal that MetS components may be more common among patients with CU.

Many mediators including TNF-α are released from mast cells of urticarial lesions (19). Studies, based on this theory, found higher TNF-α levels in CU patients, and treatments targeting TNF-α have been studied (20,21). However, some of the studies reported similar serum TNF-α levels in both CU patients and normal controls (22). Ye et al. (13) found serum TNF-α levels higher in MetS-positive CU patients. On the contrary, serum TNF-α levels were lower in our patients with CSU compared to controls. We think that local increases in TNF-α levels in wheals may not contribute to systemic inflammatory response in urticaria. In addition, similar serum TNF-α levels in both MetS-positive and negative CSU patients may suggest that various markers may be involved in development of MetS in CSU patients.

Table 3. Corelation of serum resistin level and study parameters in chronic spontaneous urticaria patients

	CSU çpatients (n=42)			
	With MetS (n=14)		Without MetS (n=28)	
	r	p*	r	p*
Duration of CSU (month)	0.34	0.24	-0.23	0.24
UAS7	-0.18	0.53	0.31	0.11
FBG (mg/dL)	-0.29	0.32	0.11	0.57
TG (mg/dL)	0.3	0.30	-0.07	0.72
HDL (mg/dL)	0.43	0.12	-0.28	0.14
LDL (mg/dL)	0.03	0.92	0.09	0.66
TNF-α (pg/mL)	0.29	0.32	0.13	0.52
Total IgE (IU/mL)	0.07	0.81	0.08	0.69

*: Spearman correlation test, CSU: Chronic spontaneous urticaria, MetS: metabolic syndrome, UAS7: Urticaria activity score over 7 days, FBG: Fasting blood glucose, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, TNF-α: Tumor necrosis factor alpha, IgE: Immunoglobulin E

Resistin is a pro-inflammatory adipokine which induces inflammation, angiogenesis, and smooth muscle proliferation (7). Serum resistin levels were reported to be associated with obesity, insulin resistance, diabetes and inflammation (7,9,11,23-25). In our study, serum resistin levels were similar in CSU patients and controls. Furthermore, resistin levels were similar in MetS-positive and negative CSU patients. This may imply that resistin may not be involved in increased inflammation of patients with urticaria.

High serum hsCRP levels are seen in MetS and studies demonstrated that increased serum hsCRP level is an important inflammatory marker in the risk of cardiovascular disease (26-29). In the CU pathogenesis, increased serum CRP level was reported and it showed positive correlation with disease activity (5,17,30). In our study, serum hsCRP level was significantly higher in CSU patients than in controls. On the other hand, although the mean serum hsCRP level was higher in MetS-positive CSU patients when compared to MetS-negative patients, the difference was not statistically significant.

Ye et al. (13) reported higher UAS score in MetS-positive patients, but UAS7 scores were higher in MetS-negative patients of our study. Any increase in UAS7 may lead to systemic inflammation, thus an increase in the risk of MetS may be expected. However, the contrary result of our study may indicate that different factors may play role in the pathogenesis of MetS and urticaria. We think that while the drugs such as systemic steroids, antihistamine, siklosporine used in the treatment of urticaria cause a decrease in urticaria activity, these treatments may also lead to deterioration in the metabolic condition. However, we could not evaluate the patient's past medications.

Similar to the study of Ye et al. (13) we found no difference in atopy presence, ANA, thyroid auto antibody positivity of MetS-positive and negative CSU patients. On the other hand, unlike their study there was no difference in ASST, serum C3-C4 levels in this study.

Conclusion

MetS was seen more common in CSU patients. However, we did not show any relationship between inflammatory markers inducing MetS development and CSU. This result suggests that there is a need for larger molecular studies to show the cause-and-effect relationship of CSU and MetS.

Ethics

Ethics Committee Approval: The ethics commitee of Eskişehir Osmangazi University Faculty of Medicine (Number: 2015/20), Informed Consent: Informed consent was signed by the volunteers.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Işıl Bulur, Design: Işıl Bulur, Zeynep Nurhan Saraçoğlu, Data Collection or Processing: Hanife Merve Akça, Işıl Bulur, Hilal Kaya Erdoğan, Analysis or Interpretation: Semra Çelebi, Literature Search: Hanife Merve Akça, Işıl Bulur, Writing: Hanife Merve Akça, Işıl Bulur.

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