Evaluation of carotid intima media thickness and hematologic inflammatory markers in patients with chronic spontaneous urticaria

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Abstract

Introduction: Low grade inflammation is associated with chronic spontaneous urticaria (CSU) and atherosclerosis. There are little data on the relationship between urticarial inflammation and atherosclerosis. The neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and mean platelet volume (MPV) have recently been studied in many diseases as a biomarker of inflammation.
Aim: To evaluate hematologic inflammatory parameters and subclinical atherosclerosis in CSU patients.
Material and methods: C-reactive protein (CRP), NLR, PLR, MPV and carotid intima media thickness (CIMT) in CSU patients were compared with healthy controls. Thirty CSU patients and 30 healthy controls participated in the study.
Results: Thirty CSU patients and 30 healthy controls participated in the study. 53.3% of the patient group were females, 46.7% were males and the mean age was 37.7 ±7.7. 53.3% of the healthy control group were females, 46.7% were males and the mean age was 37.1 ±7.2. Body mass index was 24.63 ±2.7 kg/m^2 in the patient group and 24.83 ±2.5 kg/m^2 in the control group. Left and right CIMT and CRP values were higher in CSU patients and high-density lipoproteins (HDL) values were lower in the CSU patients. There was a positive correlation between the right and left CIMT and urticaria activity severity 4 (UAS4), disease severity, and triglycerides in the patient group, also a negative correlation was found between the right and left CIMT and the HDL values. C-reactive protein was also correlated with UAS4 and disease severity.
Conclusions: This is the first study to evaluate subclinical atherosclerosis in CSU patients. Chronic spontaneous urticaria may be associated with an increased atherosclerotic risk. Serum CRP concentration can also be used as an objective parameter to evaluate disease severity.

Key words: chronic spontaneous urticaria, carotid intima media thickness, hematologic inflammatory markers.

Introduction

Chronic spontaneous urticaria (CSU) is defined as a common skin disease that is characterized by pruritus and rash that last for more than 6 weeks. Chronic spontaneous urticaria is characterized by nonspecific local inflammation accompanied by systemic acute phase response [1–3].

Inflammation is a process that has an important role in the initiation and progression of atherosclerosis and circulatory diseases [4]. Recently, inflammation has been identified as an independent risk factor for cardiovascular disease [5]. The relationship between an increased C-reactive protein (CRP) level, neutrophil activation, chronic systemic inflammation and cardiovascular disease risk has been reported in the literature [6, 7].

C-reactive protein is a well-known inflammatory biomarker and increased serum levels have been demonstrated in CSU patients [1]. In addition, it has been shown in the studies that levels of acute phase response (APR)-associated inflammatory markers such as CRP, interleukin 6 (IL-6), tumor necrosis factor α (TNF-α) and matrix metalloproteinase 9 in the circulation increase in CSU. In addition, good correlations of these inflammatory markers with urticaria activity and severity score have been reported [1, 8–10].

In recent years, it has been shown that the neutrophil lymphocyte rate (NLR) and platelet lymphocyte rate (PLR)

which are the ratio of neutrophil and platelet counts to lymphocyte counts, are indicative of systemic inflammation and are associated with prognosis in many cardiovascular diseases, malignancies and chronic inflammatory diseases [1, 11–13]. Mean platelet volume (MPV) is considered to be a marker of platelet function and activation, and high MPV values have been shown to be independent risk factors for acute myocardial infarction. In addition, it has been reported that MPV value is high in some systemic inflammatory diseases and has a positive correlation with CRP [14].

In recent years, the emphasis has been laid on the measurement of carotid artery intima media thickness (CIMT) with carotid artery ultrasound in the evaluation of subclinical atherosclerosis. A CIMT increase is considered to be a marker of atherosclerosis [15]. It was first identified in 1986 by Pignoli *et al.* and there are many literature studies available today [16, 17].

Chronic spontaneous urticaria patients have been reported to have a significantly higher prevalence of the metabolic syndrome when compared to the age-matched control group [18]. The existence of metabolic syndrome often increases the cardiovascular disease risk. Studies show that diseases with chronic inflammation (psoriasis, psoriatic arthritis, Behçet's disease, etc.) pose a risk in terms of atherosclerosis [19].

Aim

There are little data on the relationship between urticarial inflammation, atherosclerosis and the cardiovascular disease risk. The aim of our study is to examine the hematologic inflammatory marker (NLR, PLR, MPV) and CRP levels in patients with CSU and to evaluate the risk of subclinical atherosclerosis by measuring the thickness of carotid intima media and to determine the correlation of these findings with disease severity and duration.

Material and methods

Patients

Thirty CSU volunteer patients (15 ASST+, 15 ASST–) who were followed-up in the chronic urticaria polyclinic of the Ministry of Health Sakarya University Training and Research Hospital and who met the inclusion criteria, and 30 healthy controls who came to the dermatology clinic for causes other than chronic inflammatory diseases and who have not had an urticaria attack before they were enrolled in the study. A local ethics committee approval was obtained before the study (SÜEK.16214662/05.01.04/82).

Patients and controls with classical cardiovascular risks were excluded from the study. In addition, so were those who have a history of cardiovascular, cerebrovascular and peripheral artery disease, collagen tissue disease, systemic vasculitis, autoimmune diseases, thyroid disease, systemic disease and malignancy, those who receive antihyperlipidemic, antihypertensive, antiaggregant, anticoagulant, nitrate, estrogen and oral contraceptive treatment, those who smoke and use alcohol, pregnant women, those who are < 18 years of age and > 50 years of age. Cardiovascular risk factors include hypertension (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, diabetes mellitus (fasting blood glucose: > 110 mg/dl), hyperlipidemia (total cholesterol > 240 mg/dl and/or TG > 160 mg/dl), serum creatinine value > 1.3 mg/dl and obesity (body mass index > 30 kg/m^2).

Evaluation of disease severity

Urticaria activity score (UAS) was evaluated on the day of blood-letting (rash number: no rash: 0, 1–10 wheals = 1, 11–50 wheals = 2, > 50 wheals = 3+ pruritus intensity: none: 0, mild: 1, moderate: 2, severe: 3; minimum = 0, maximum = 24). UAS was graded as mild (1–8), moderate (9–16) and severe (17–24).

Autologous serum test

The autologous serum test was applied only to the patient group on the sample blood-letting day. 0.05 ml of autologous serum was given to the inner side of the forearm. Similarly, sterile saline was applied at the same dose as negative control. Thirty minutes after the application, an erythematous urticarial papule formation of 1.5 mm or greater from negative control was positively evaluated.

Detailed anamnesis-taking and physical examination of all patients were performed. Venous blood samples were taken for hemogram, CRP, total cholesterol, triglyceride, high-density lipoproteins (HDL), low-density lipoproteins (LDL), fasting blood sugar, urea, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) determination.

Carotid artery Doppler US evaluation

Intima media thickness (IMT) measurement software was used by the same radiologist for the measurement of carotid artery intima media thickness of all subjects included in the study with high resolution color Doppler ultrasonography (Toshiba aplio 400, Otawara-shi, Japan) with PLT-1204 BX transducer (7.2–14 MHz). Intima media thickness was measured from CCA, Bulb and ICA levels on both sides and carotid intima media thickness was calculated by the device.

Statistical analysis

Statistical analyses were evaluated using the Statistical Package for Social Sciences for Windows version 17.0 (SPSS, Chicago, IL, USA) program. Descriptive data were expressed as mean ± standard deviation, numbers and percentages. Student's *t*-test was used to compare continuous data. χ^2 test was used to compare categori-

cal data. The relationship between continuous data was evaluated by Pearson correlation test.

$P < 0.05$ value was considered as the level of significance. Negative values show an inverse correlation and positive values show a positive correlation in the correlation evaluation.

Results

Thirty CSU patients and 30 healthy controls participated in the study. 53.3% of the patient group were females, 46.7% were males and the mean age was 37.7 ±7.7. 53.3% of the healthy control group were females, 46.7% were males and the mean age was 37.1 ±7.2. Body mass index (BMI) was 24.63 ±2.7 kg/m^2 in the patient group and 24.83 ±2.5 kg/m^2 in the control group. The mean disease duration of chronic urticaria patients was determined as 40.24 ±35.36 months. The average UAS was 16.87 ±4.0. There was no statistically significant difference in terms of age, sex and BMI distribution in both groups (Table 1).

The HDL values were found to be significantly lower in the CSU group as compared to healthy controls, but there was no significant difference between the two groups in terms of LDL, total cholesterol and triglicerydes (TG) values. The CRP level was significantly higher in the CSU group as compared to the control group, but there was no significant difference between two groups in terms of MPV, platelets (PLT), NLR, and PLR. Right and left CIMT scores were 0.54 ±0.08, 0.53 ±0.1 in the CSU group and 0.48 ±0.07, 0.46 ±0.09 in the control group, respectively. Right and left CIMT scores were found to be statistically significantly increased in patients with CSU compared to healthy controls (Table 2). There was no correlation between right and left CIMT and UAS4, duration of the disease, disease severity, CRP, MPV, NLR, PLR, LDL, total cholesterol and BMI in the patient group. However, a significant positive but inverse correlation was found between the right CIMT and the HDL value, and also a significant and positive correlation with TG value. In addition, there was a positive correlation between left CIMT and TG value (Table 3).

Table 1. Demographical data of the chronic spontaneous urticaria (CSU) and control groups

Parameter		CSU	Healthy controls	t	P-value
Gender, n (%)	Female	16 (53.3)	16 (53.3)	–	–
	Male	14 (46.7)	14 (46.7)	–	–
Age, mean ± SD [years]		37.7 ±7.7	37.1 ±7.2	0.52	0.959
BMI, mean ± SD [kg/m^2]		24.63 ±2.7	24.83 ±2.5	0.297	0.768
UAS, mean ± SD		16.93 ±4.32	–	–	–
Disease duration, mean ± SD [months]		40.2 ±35.36	–	–	–

BMI – body mass index.

Table 2. Laboratory findings and CIMT in the CSU and control groups

Parameter	CSU (n = 30) Mean ± SD	Healthy controls (n = 30) Mean ± SD	P-value
HDL	50.00 ±9.82	59.70 ±12.60	0.002*
Total cholesterol	176.73 ±19.42	169.70 ±26.82	0.249
LDL	100.13 ±16.80	97.00 ±19.50	0.508
TG	101.07 ±33.87	88.53 ±36.69	0.174
CRP	4.96 ±4.06	0.80 ±0.65	< 0.0001*
MPV	7.72 ±0.84	8.39 ±2.16	0.124
PLT	268.2 ±62.19	261 ±60.4	0.689
NLO	2.19 ±0.94	2.91 ±5.00	0.445
PLO	124.13 ±44.19	117.60 ±35.64	0.530
Right CIMT	0.52 ±0.09	0.48 ±0.07	0.043*
Left CIMT	0.55 ±0.08	0.50 ±0.07	0.012*

$P < 0.05$ level of significance. CSU – chronic spontaneous urticaria, CRP – C-reactive protein, NLR – neutrophil lymphocyte ratio, HDL – high-density lipoprotein, LDL – low-density lipoprotein, PLR – platelet lymphocyte ratio, TG – triglycerides, MPV – mean platelet volume, right CIMT – right carotid intima media thickness, left CIMT – left carotid intima media thickness.

Table 3. Change of CIMT and CRP with disease duration, UAS, disease severity and laboratory findings

Parameter	Right CIMT		Left CIMT		CRP	
	R	*P*-value	*R*	*P*-value	*R*	*P*-value
Total cholesterol	0.275	0.142	0.141	0.457	0.00	0.998
BMI	0.272	0.145	0.345	0.062	0.311	0.094
HDL	−0.484	0.007*	−0.361	0.050*	−0.460	0.010*
LDL	0.498	0.005*	0.249	0.184	0.194	0.304
TG	0.461	0.01*	0.498	0.05*	0.394	0.031*
CRP	0.397	0.03*	0.427	0.019*	–	–
NLR	0.0061	0.748	0.126	0.509	0.195	0.301
PLR	0.038	0.842	0.050	0.794	0.129	0.498
UAS	0.365	0.047*	0.417	0.022*	0.427	0.019*
Severity of disease	0.436	0.016*	0.474	0.008*	0.486	0.006*
Disease duration	0.245	0.192	0.083	0.662	−0.123	0.516

*Correlation is significant at the 0.05 level. CRP – C-reactive protein, NLR – neutrophil lymphocyte ratio, HDL – high-density lipoprotein, LDL – low-density lipoprotein, PLR – platelet lymphocyte ratio, TG – triglycerides, BMI – body mass index, UAS – urticaria activity severity, right CIMT – right carotid intima media thickness, left CIMT – left carotid intima media thickness.

A statistically significant correlation was determined between CRP value and UAS and disease severity in the patient group. There was also a significant positive but inverse correlation between CRP and HDL values and a significant positive correlation with TG value. However, there was no correlation between duration of disease, MPV, NLR, PLR, LDL, and total cholesterol (Table 4).

There was no significant difference between the ASST positive and ASST negative patient groups in terms of CRP, NLR, PLR, MPV, total cholesterol, TG, HDL, LDL, right and left CIMT.

Discussion

We found that right and left CIMT values were statistically significantly higher in the CSU group as compared to the healthy control group and HDL values were significantly lower in the CSU patients as compared to the healthy control group and the CRP values were significantly higher in the CSU patient group. There was also a statistically significant positive correlation between CRP value and UAS, disease severity, and TG in the patient group, and a significant but inverse correlation with HDL. In addition, there was a significant but inverse correlation between right CIMT and HDL value, and a significant and positive correlation between right and left CIMT and TG value.

Chronic spontaneous urticaria is a persistent inflammatory disease of the skin characterized by non-necrotizing infiltration of CD4+ lymphocytes consisting of mast cell degranulation and perivascular Th1 and Th2 subtypes as well as monocytes, neutrophils, eosinophils and basophils [1], but there is little information currently available on the skin infiltration with such cells in CSU and the

Table 4. Laboratory findings and CIMT in ASST+ and ASST– patient group

Parameter	ASST+ (*n* = 15) Mean ± SD	ASST – (*n* = 15) Mean ± SD	*P*-value
HDL	52.47 ±8.43	47.53 ±10.75	0.173
Total cholesterol	178.2 ±16.77	175.27 ±22.25	0.687
LDL	101.13 ±15.53	99.13 ±18.47	0.751
TG	103.13 ±36.28	99.00 ±32.42	0.745
CRP	5.73 ±3.74	5.73 ±4.10	0.995
MPV	7.25 ±0.82	7.60 ±1.02	0.301
PLT	284.60 ±84.420	251.80 ±17.551	0.152
NLO	1.95 ±0.693	2.44 ±1.11	0.159
PLO	128.10 ±49.37	120.19 ±39.67	0.632
Right CIMT	0.54 ±0.07	0.55 ±0.09	0.893
Left CIMT	0.51 ± 0.09	0.53 ±0.09	0.672

ASST – Autologous Serum Skin Test, CRP – C-reactive protein, NLR – neutrophil lymphocyte ratio, HDL – high-density lipoprotein, LDL – low-density lipoprotein, PLR – platelet lymphocyte ratio, TG – triglycerides, BMI – body mass index, UAS – urticaria activity severity, MPV – mean platelet volume, right CIMT – right carotid intima media thickness, left CIMT – left carotid intima media thickness.

warning that is responsible for that and systemic inflammatory response [1].

C-reactive protein is the most intensively studied inflammatory marker. C-reactive protein is an acute phase protein produced by main hepatocytes under the influence of cytokines such as TNF-α and IL-6 [20]. Danesh *et al.* [21] have found that even slight elevations in CRP concentrations between normal laboratory values may be associated with an increased cardiovascular risk. It has

also been reported that the concentration of CRP increases in circulation in CSU patients [22]. Kasperska-Zajac et al. [22] have reported a positive correlation between CRP levels and urticaria severity and CRP levels, as well as the increase in CRP levels in CSU patients. Another study by Kasperska-Zając et al. [22] has reported that IL-6 and CRP levels were increased in CSU patients, and there is a correlation between IL-6, CRP and UAS. In addition, they have observed that IL-6 and CRP level decreased in spontaneous remission [8]. In our study, we found that CRP levels were significantly increased in CSU patients in line with previous studies. We also observed a correlation between CRP levels and UAS and disease severity. These findings support the previous findings reporting that CSU showed low grade inflammatory symptoms [1, 8, 22]. It also supports that serum CRP concentration may be an objective parameter in evaluating disease severity in CSU.

During systemic inflammation, neutrophil activation and increased NLR reactive oxygen derivatives lead to the release of cytokines (IL-1RA, IL-6, IL-7, IL-8, IL-12), proteases and cationic proteins (such as elastase and lactoferrin) [6]. Neutrophil activation products have been shown to be associated with severity of various inflammatory diseases. It has been reported in recent years that neutrophils and associated lymphopenia are independent determinants of mortality in cardiovascular diseases and furthermore, NLR has been shown to be an inflammation indication in cardiac and non-cardiac diseases [3, 6, 23–25]. Karabay et al. [26] have reported significantly higher NLR values also in CSU patients as compared to healthy controls and also have found a positive correlation between serum CRP values and NLR values in CSU patients. However, they have observed no correlation between clinical disease severity and NLR value [26]. In our study, there was no significant difference in NLR values between the patient group with CSU and the control group, and there was no correlation between CRP and NLR values in the patient group.

The platelets interact with endothelial cells, leukocytes (monocytes, neutrophils, dendritic cells, T-cells) and progenitor cells in addition to their function of providing hemostasis, allowing the inflammatory cells to migrate to the lesion areas, causing abundant amounts of inflammatory cytokines to be released and eventually create an inflammatory environment in the lesion area. Platelets contribute to the formation of atherosclerotic plaques with surface receptors they express and the cytokines they secrete or to endothelial damage leading to thrombotic complications together with other components of inflammation [27]. It has been reported in recent years that MPV also reflects platelet function and activation and may be a marker of inflammation in different chronic diseases. It has also been shown that high PLR, as in NLR, is associated with mortality in cardiac diseases [13, 14, 27]. We did not find a significant difference between the

MPV and PLR values in the CSU patient group compared to the healthy controls, and we found no significant correlation between MPV, PLR and CRP in the CSU patient group. We did not find any studies evaluating PLR in CSU in the literature. As far as we know, this is the first study to evaluate PLR in CSU. Similar MPV values determined in our study in CSU patients and in the healthy control group were similar to those of Zajac et al., but were not consistent with other studies that reported increases or decreases in MPV values [28–31].

Magen et al. [29] have reported in their study consisting of 373 patients with CSU and 46 healthy controls that increased MPV values might be an indicator of increased disease activity severity in patients with ASST-positive CSU. Akelma et al. [31] have reported significantly lower MPV in pediatric patients compared to healthy controls.

These changes between studies may result from technical reasons and from different criteria used in the classification of patients. Especially in retrospective analyses, it may be due to failure to apply exclusion criteria including DM, HT, obesity, smoking, arterial and autoimmune disease. Lately, almost all diseases can increase or reduce MPV. Therefore, the practical possibility of excluding MPV-related diseases and conditions completely is difficult.

We did not find NLR, PLR and MPV values in CSU patients to be similar to those of healthy controls and not to be associated with CRP and disease severity in the CSU patient group. We therefore believe that MPV, NLR and PLR values are insufficient data for evaluating inflammation and disease severity in CSU. However, there is a need for more larger-scale prospective studies on the use of these parameters in CSU.

Studies show that skin diseases with chronic inflammation such as psoriasis and psoriatic arthritis pose a risk of atherosclerosis [19, 32]. Inflammation has an important role in the initiation and progression of atherosclerosis and circulatory diseases. Atherosclerosis is a chronic inflammatory and immunological disease in which many cells, including monocytes, macrophages, T lymphocytes, endothelial cells, smooth muscle cells and mast cells, are included [4]. Chronic spontaneous urticaria is thought to be a chronic inflammatory disease with cutaneous mast cell degranulation, T-cell, eosinophil, and neutrophil infiltration [1]. It has been shown that low-grade inflammation is associated with atherosclerosis and CSU. TNF-α, IL-1-IL-2, IL-6, IL-8, IL-12, IL-18 are shown to be cytokines responsible for atherosclerotic plaque formation [4]. Increase in IL-6, TNF-α, IL-1B, IL14, IL-13 and IL-18 levels were also observed in CSU patients [8–10, 33, 34]. Moreover, it is assumed that CSU is a nonallergic disease induced by activation of mast cells thought to be significantly associated with hyperlipidemia and atherosclerosis. Mast cells participate in both the natural and adaptive immune system and they play an important role in maintaining healthy physiology in wo-

und healing angiogenesis. There is considerable evidence that mast cells play a key role in inflammation and that their products regulate inflammatory mediator production [35]. In recent years, mast cells have been shown in atherosclerotic plaque development and inflammatory disease processes such as cardiovascular disease, hyperlipidemia [36–38]. The mast cells present in the human arterial intima may be degranulated after stimulation and secrete the chymase inhibiting HDL apolipoprotein and delay cellular cholesterol flow. In fact, Lee *et al.* [39] have reported that mast cell chymase disrupts and decreases the level of APOA-1, the major HDL apolipoprotein that changes lipid metabolism.

In addition, the clinical effects and prevalence of metabolic syndrome among CSU patients was investigated in a hospital-based comparative cross-sectional study of 131 CSU patients and a higher prevalence of metabolic syndrome have been found in CSU patients [18]. They have reported that the presence of the metabolic syndrome in the logistic regression analysis correlated with a high urticaria activity score and that it was an independent risk factor for uncontrolled CSU. In another community-based cross-sectional study of 11261 CSU patients, the relationship between CSU and the metabolic syndrome has been investigated and in univariate analysis CSU has been found to be associated with higher metabolic syndrome and its components which are DM, obesity, hyperlipidemia and hypertension prevalences [40].

In recent studies, the measurement of intima media thickness with carotid artery USG, which is an inexpensive, simple and easily acceptable method for evaluating subclinical atherosclerosis, has been focused on [41]. Intima media thickness increase is considered as an atherosclerosis marker [15]. 0.1 mm increase in CIMT increases the myocardial infarction risk by 10–15% and the stroke risk by 13–18% [42].

In the light of this, it can be argued that when CSU is considered as an inflammatory disease, these patients may have an increased risk of atherosclerosis. In our study, we found that the values of right and left carotid intima media thickness were statistically significantly higher and the HDL value was significantly lower in CSU patients who did not have any known cardiovascular risk factor compared to the healthy control group. There was also an inverse correlation between CRP value and HDL and a positive correlation between these and TG in the CSU group. These findings support that there may be an increased risk of atherosclerosis in CSU patients. Our study is the first in the literature to investigate subclinical atherosclerosis in CSU patients. Having a small number of samples is the limiting factor of our study.

Conclusions

We are of the opinion that serum CRP concentration may be an objective parameter in evaluating disease se-

verity in CSU but there are not sufficient data for the use of NLR, MPV and PLR in evaluating CSU inflammation and disease severity. On the other hand, we think that there is a need for larger-scale prospective studies on the use of these parameters in CSU. Furthermore, according to our results, impairment of lipid metabolism and atherosclerosis may be an increased trend in CSU patients, but more comprehensive prospective studies are needed to better define the relationship between the verification of these data and urticaria atherosclerosis.

Conflict of interest

The authors declare no conflict of interest.

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