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Circulating Pentraxin-3 and its association with C-reactive protein levels and disease activity in patients with chronic spontaneous urticaria

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Abstract

Introduction: Pentraxin-3 (PTX3) is a soluble long pentraxin molecule that regulates inflammatory responses. This study aimed to determine the plasma levels of plasma PTX-3 as an inflammation marker in chronic spontaneous urticaria (CSU) and whether the PTX3 levels correlate with disease activity and other clinical parameters, including acute phase reactants and biomarkers. **Methods:** The study included 70 CSU patients and 30 healthy controls. Plasma PTX3 levels were measured by ELISA. CSU disease activity was evaluated with the urticaria activity score summed over 7 days. Complete blood count, C-reactive protein (CRP), transaminases, total IgE, antinuclear antibody, anti-thyroid peroxidase, anti-thyroglobulin, and D-dimer levels were recorded. **Results:** Of the 70 patients, 52 (74.3%) were female, with a mean age of 37.51 ± 11.80 years. Disease activity was severe in 43, moderate in 15, and mild in 12 patients. Mean PTX3 levels were elevated in CSU patients compared to healthy controls (0.81 vs. 0.55 ng/mL, $p = 0.031$). The mean CRP levels were higher in patients than in the controls (4.26 vs. 1.57 mg/L, $p = 0.023$). Patients also had higher D-dimer levels than the controls (5.96 vs. 0.59 mg/L, $p < 0.001$). A significant positive correlation was found between PTX3 and CRP levels ($r = 0.508$, $p < 0.001$) and between D-dimer levels and UAS7 ($r = 0.338$, $p = 0.004$) and CRP ($r = 0.213$, $p = 0.034$) levels. A multivariable stepwise regression analysis showed that the one-unit increase in the CRP level increased to 38.19 units in the PTX3 level (95% confidence interval [17.40-58.98], $p < 0.001$). **Conclusion:** Circulating levels of CRP and PTX3, two members of the pentraxin family, are significantly correlated and elevated in CSU patients with increasing disease activity, indicating their utility as inflammatory markers in CSU.

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Introduction

Chronic spontaneous urticaria (CSU) is a chronic inflammatory skin disorder characterized by the occurrence of migratory skin transient pruritic wheals (hives), with or without accompanying angioedema, for 6 weeks or longer in the absence of an identifiable trigger.¹ CSU is a common condition that affects 1-2% of the general population and is more prevalent in adults, particularly women.^{2,3} Several mechanisms, such as auto-allergy, auto-immunity, coagulation, complement system, drugs, emotional stress, foods and food additives, genetics, infections, inflammation, and intestinal dysbiosis, have been implicated in CSU etiopathogenesis.³⁻⁵ Moreover, alterations in circulating levels of coagulation-fibrinolytic factors, hormonal and metabolic markers, and inflammatory mediators have been reported in CSU patients.⁶⁻⁸ Degranulation of cutaneous mast cells is involved in CSU pathogenesis by initiating skin alterations, inducing recruitment of basophils, monocytes, eosinophils, and T cells to the lesion site, and causing sensory nerve stimulation, vasodilation, and extravasation.⁹ Yet, exact mechanisms underlying CSU pathogenesis remain largely elusive.

Pentraxins (PTXs) are a superfamily of evolutionarily conserved soluble pattern recognition proteins with immune-modulatory roles.^{10,11} C-reactive protein (CRP) and serum amyloid P component, which are major acute phase proteins, are short PTXs mainly produced by hepatocytes in response to systemic inflammatory mediators such as interleukin (IL)-6.¹⁰ CRP has been proposed and frequently used as a biomarker of disease activity and response to treatment in CSU.¹² CRP levels are often found to be elevated in CSU, albeit at a lower level than in other autoimmune and inflammatory diseases, and strongly correlate with the disease activity and other inflammatory markers, such as erythrocyte sedimentation rate (ESR), leukocyte counts, and serum IL-6 levels.^{6,12,13} Pentraxin-3 (PTX3), a long PTX, is produced locally by various cell types, such as endothelial, epithelial cells, and fibroblasts, at the site of infection or inflammation.^{10,11,14,15} It regulates innate immunity by facilitating pathogen recognition, complement system activation, and tissue remodeling and repair.^{10,16,17} Several studies have indicated the utility of PTX3 as a highly sensitive and independent inflammatory marker and its association with the severity of various conditions in humans, such as autoimmune diseases, cardiovascular diseases, infections, inflammatory bowel diseases, malignancies, metabolic syndrome, obesity, respiratory diseases, and preeclampsia.¹⁵⁻¹⁸ In addition, PTX3 has been demonstrated to reciprocally regulate the expression of proinflammatory cytokines in mast cells.¹⁹

Given the implication of the pentraxin superfamily in inflammatory conditions, in particular, CRP in CSU, there has been so far only one study regarding the involvement of PTX3 in CSU,²⁰ in which circulating PTX3 levels were reported to be increased in severe CSU patients from Poland. Nevertheless, studies focusing on the correlation between the circulating PTX3 and other inflammatory markers in patients with different ethnic backgrounds remain limited. Thus, we aimed to evaluate the plasma

PTX3 levels and their association with serum CRP levels and disease severity in CSU patients from Turkey.

Materials and Methods

Patient recruitment and ethics

This prospective study consisted of 100 participants, including 70 adult patients with CSU (older than 18 years) diagnosed based on the recent guideline¹ and 30 age- and sex-matched healthy individuals. This study was conducted by the World Medical Association Declaration of Helsinki and approved by the İhsan Doğramacı Bilkent University Human Research Ethics Committee (#2022_12_03_01) with written informed consents obtained from all individual participants. Patients (i) with known inflammatory or autoimmune disease, infection, cardiovascular disease, chronic renal disease, coagulation disorders, malignancy, or pregnancy, (ii) receiving anticoagulant or immunosuppressant therapies, and (iii) with chronic inducible urticaria only or urticarial vasculitis were not included in the study. Patients' demographic features and clinical details, such as disease duration/activity, triggering factors, medications, therapeutic response, and time to remission, were obtained from the clinical assessment records and collected during the study period. CSU disease activity was evaluated utilizing the urticaria activity score summed over 7 days (UAS7), a validated simple scoring system that assesses wheals and pruritus.¹ Accordingly, UAS7 scores of 6 and below were accepted as well-controlled, 7-15 as mild, 16-27 as moderate, and 28-42 as severe disease. The therapeutic response was determined based on the antihistamine doses used by the patients and the need for other drugs such as montelukast, methylprednisolone, cyclosporine-A, or omalizumab. Patients who did not respond to 4-fold doses of second-generation H1-antihistamines were categorized as antihistamine-refractory cases.

Biochemical measurements

Complete blood counts, CRP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total IgE, anti-nuclear antibody (ANA), anti-thyroid peroxidase (TPO), anti-thyroglobulin (TG) and D-dimer levels, and thyroid function and renal function tests were investigated during the detailed routine control visits of the patients at the hospital. The results of serological tests were analyzed by an automated analyzer. Results were accepted as positive if anti-TPO titer > 60 U/mL, anti-TG titer ≥ 4.5 IU/mL, and D-dimer titer ≥ 0.55 mg/L. The normal reference range for CRP is 0-≤5 mg/L. Plasma was separated from peripheral venous blood samples of patients and healthy controls and stored at -80°C for future use. Plasma PTX3 levels were measured by commercially available enzyme-linked immunosorbent assay (ELISA) following the manufacturer's instructions (BioLegend ELISA MAX™ Deluxe Set Human PTX3). This set's expected minimum detectable concentration of human PTX3 is 17.1 pg/ml. Briefly, 96-well plates were coated with diluted PTX3 Capture antibody (1:200) in 1× Coating Buffer and incubated overnight at

4°C. After incubation, plates were washed four times with Wash Buffer and blocked with 1× Assay Diluent B at room temperature for 1 h with shaking on a plate shaker. After washing the plates, plasma samples diluted in 1× Assay Diluent B (1:3) and recombinant human PTX3 as standards prepared in 1× Assay Diluent B were added onto the wells in duplicates and incubated at room temperature for 2 h with shaking. Plates were washed four times and incubated with diluted Detection Antibody solution (1:200) in 1× Assay Diluent B at room temperature for 1 h with shaking. After washing the plates, diluted Avidin-HRP solution (1:1000) in Assay Diluent B was added to each well and incubated at room temperature for 30 min with shaking. Plates were washed five times, and TMB Substrate Solution was added to each well, followed by incubation in the dark for 15 min. The reaction was stopped by adding the Stop solution (H₂SO₄). Absorbance in wells was measured at 450 nm and 570 nm by using a microplate reader (Synergy, BioTek). The absorbance at 570 nm was subtracted from the absorbance at 450 nm. Data were analyzed using a 4-parameter logistic curve.

Statistical analysis

All statistical analyses were performed using the SPSS 25.0 package program (SPSS Inc., Armonk, NY, USA). Data are presented as mean ± standard deviation (SD), mean ± standard error of the mean (SEM), median ± interquartile range (IQR), or frequency (%). The Kolmogorov-Smirnov test was performed to determine the normality of distribution. The chi-square test was used to compare categorical parameters. The Independent Samples T-test or Mann-Whitney U test was used to compare normally or non-normally distributed continuous variables. ANOVA or Kruskal Wallis tests were utilized for comparing the differences between three or more groups. To determine the factors affecting PTX3 levels, regression analysis was performed. The statistical significance of the correlation was determined with Pearson's or Spearman's correlation test, depending on the normality. The correlation power was weak if $r < 0.2$, weak if $r = 0.2-0.4$, moderate if $r = 0.4-0.6$, strong if $r = 0.6-0.8$, and very strong if $r > 0.8$. p -values less than 0.05 were considered significant. GraphPad Prism software (San Diego, CA, USA) was used for graphical analysis.

Results

Seventy patients and 30 healthy controls were included in the study. Of the 70 patients, 52 (~74%) were female with a mean age ± SD of 37.51 ± 11.80 years. Of the 30 controls, 22 (~73%) were female with a mean age ± SD of 33.70 ± 8.96 years. The average body mass index (BMI) of individuals was around 25 kg/m² in both the patient and control groups. Overall, there was no significant difference between the patient and control groups in terms of mean age ($p = 0.11$), gender ratio ($p = 0.96$), or mean BMI ($p = 0.56$). The median duration of urticaria was 12 (IQR: 6-24) months. Urticaria was accompanied by angioedema in 53 (~76%) patients. Twenty-eight patients had accompanying physical urticaria, with symptomatic dermatographism

($n = 13$) as the most common type. Urticaria triggers were reported as stress in 44 (~63%) patients, non-steroidal anti-inflammatory drugs in 6 (~9%) patients, and food and food additives in 7 (10%) patients. Regarding the treatments received by the patients, only 12 (19%) patients used a regular dose of non-sedating second-generation antihistamine. In contrast, 7 patients received two doses/day, 3 patients received three doses/day, and the remaining patients ($n = 48$) received four doses/day. During the follow-up of the patients, 18 patients needed steroid treatment for at least 10 days to control the disease, and 15 patients needed add-on therapies (montelukast for 1 patient; omalizumab for 14 patients) in addition to the four-fold antihistamine doses. Cyclosporin-A was used in patients ($n = 2$) who did not respond to omalizumab. When disease activity was evaluated, it was observed that 43 (61.4%) patients had severe disease, 15 (21.4%) patients had moderate disease, and 12 (17.1%) patients had mild disease. The median UAS7 scores of patients were 34 (IQR: 20-42 points). Moreover, none of the patients had ANA positivity. Thirteen (20.6%) CSU patients were positive for Anti-TPO and Anti-TG but had no thyroid disease, whereas three individuals were positive for only Anti-TG in the control group. Lastly, no parasite or *H. pylori* antigen was detected in stool samples in any patients. The demographic and clinical characteristics of CSU patients are presented in Table 1.

Next, we tested whether plasma PTX3 levels differed in CSU patients compared to healthy individuals. It was previously reported that circulating PTX3 levels were increased only in some CSU patients, particularly patients with moderate to severe CSU.²⁰ However, we found significantly elevated plasma PTX3 levels in CSU patients, including mild, moderate, and severe disease groups as a whole (mean: 0.81 ng/mL) compared to the healthy controls (mean: 0.55 ng/mL) ($p = 0.031$) (Figure 1A). The mean plasma PTX3 concentrations of patients with mild ($n = 12$), moderate ($n = 15$), and severe ($n = 43$) CSU were 0.50 ng/mL, 0.79 ng/mL, and 0.89 ng/mL, respectively, indicating a rise in PTX3 levels with increasing disease severity. In particular, mean PTX3 levels were significantly higher in the severe disease group than in the mild disease group ($p = 0.02$), consistent with the previous report.²⁰ Moreover, mean plasma PTX3 levels in antihistamine-resistant patients (1.08 ng/mL), patients with physical urticaria (0.87 ng/mL), and patients with angioedema (0.82 ng/mL) were increased compared to antihistamine responders (0.72 ng/mL), patients without physical urticaria (0.68 ng/mL), and patients without angioedema (0.78 ng/mL), respectively, but these elevations were not statistically significant ($p > 0.05$). Finally, we checked whether PTX3 levels differ between females and males. Mean plasma PTX3 levels were lower in males than females among CSU patients (0.70 ng/mL vs. 0.84 ng/mL) and healthy controls (0.37 ng/mL vs. 0.62 ng/mL). Yet, this difference was statistically significant only in the control group ($p = 0.01$).

As expected, patients with CSU had elevated serum CRP levels compared to the controls (mean: 4.26 mg/L vs. 1.57 mg/L, $p = 0.007$) (Figure 1B). Serum CRP levels seemed to increase with the severity of the CSU patients, with mean values of 3.61 mg/L, 4.30 mg/L, and 4.42 mg/L in mild, moderate, and severe diseases, respectively. However, there were no significant differences in

Table 1 Demographic and clinical characteristics of the study groups.

Demographic and clinical features	Controls (n = 30)	Patients (n = 70)	P
Age (year) (mean ± SD)	33.70 ± 8.96	37.51 ± 11.80	0.11
Body mass index (kg/m ²) (mean ± SD)	25.03 ± 4.61	25.73 ± 4.66	0.56
Gender (n, %)			0.96
	Female	22 (73.3%)	
	Male	8 (26.7%)	
Urticaria duration (month) (median, IQR)	—	12 (6-24)	—
Disease activity			
	Mild	12 (17.1%)	—
	Moderate	15 (21.4%)	—
	Severe	43 (61.4%)	—
Angioedema accompanying urticaria	—	53 (75.7%)	—
Types of physical urticaria			
	Cold	2 (2.9%)	—
	Heat	1 (1.4%)	—
accompanying CSU			
	Vibratory	1 (1.4%)	—
	Aquagenic	1 (1.4%)	—
	Delayed pressure	10 (14.3%)	—
	Symptomatic dermatographism	13 (18.6%)	—
Anti-TPO and Anti-TG positivity	3 (10%)	13 (20.6%)	0.22

IQR: Interquartile range, SD; Standard deviation, CSU; Chronic spontaneous urticaria, Anti-TPO; Antithyroid peroxidase, Anti-TG; Anti- thyroglobulin.

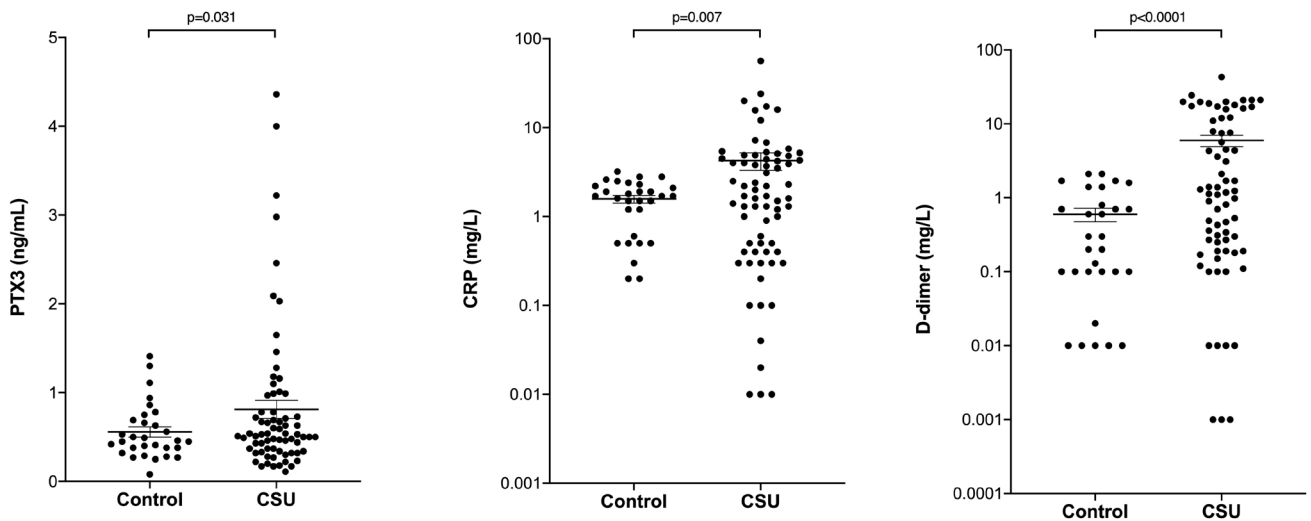


Figure 1 Plasma pentraxin 3 (PTX3), CRP, and D-dimer levels in patients with chronic spontaneous urticaria (CSU) (n = 70) and healthy controls (n = 30). Graphs are shown on a base-10 logarithmic or linear scale present mean expression levels ± standard error of the mean.

CRP levels between CSU patients with different disease severities ($p > 0.05$). Moreover, the mean serum D-dimer level of the patients (5.96 mg/L) was significantly higher than the control group (mean: 0.59 mg/L) ($p < 0.0001$) (Figure 1C). In particular, patients with severe CSU had significantly increased levels of D-dimer (mean: 8.33 mg/L) than patients with moderate (mean: 2.76 mg/L, $p = 0.01$) or mild (mean: 1.48 mg/L, $p < 0.0001$) diseases, and healthy controls (mean: 0.59 mg/L, $p < 0.0001$). Levels of Anti-TPO, Anti-TG, and total IgE in patients were also significantly elevated compared to the healthy controls (Table 2) but did not differ statistically with disease severity ($p > 0.05$). Finally, no significant differences between the CSU patients

and the healthy controls regarding lymphocyte, neutrophil, basophil, eosinophil, platelet counts, and transaminase levels were found. The laboratory findings of patients with CSU and healthy controls are presented in Table 2.

We next performed correlation analyses and found a significant positive correlation between PTX3 and CRP levels ($r = 0.508$, $p < 0.0001$), consistent with the previous study,²⁰ whereas a negative correlation between PTX3 and PLT levels ($r = -0.293$, $p = 0.003$). Although there was not any correlation between D-dimer and PTX3 levels, we found a positive correlation between D-dimer level and UAS7 ($r = 0.338$, $p = 0.004$), total IgE level ($r = 0.370$, $p = 0.043$) and CRP level ($r = 0.213$, $p = 0.034$) and a negative

Table 2 Laboratory findings in patients and control groups.

Variables	Controls (n = 30)	Patients (n = 70)	P value
PTX3, ng/mL	0.55 ± 0.05	0.81 ± 0.10	0.031
CRP, mg/L	1.57 ± 0.15	4.26 ± 0.94	0.007
D-dimer, mg/L	0.59 ± 0.12	5.96 ± 1.04	<0.0001
LYM, x10 ⁹ /L	2483.66 ± 122.20	2225.00 ± 77.52	0.08
NEU, x10 ⁹ /L	4648.40 ± 200.50	4687.85 ± 235.18	0.89
BAS, x10 ⁹ /L	33.13 ± 2.85	26.61 ± 3.11	0.12
EOS, x10 ⁹ /L	170.10 ± 27.52	160.80 ± 17.79	0.77
PLT, x10 ⁹ /L	299833.33 ± 7687.29	287214 ± 8701.41	0.28
ALT, U/L	19.43 ± 1.39	22.10 ± 1.73	0.23
AST, U/L	21.60 ± 1.58	20.94 ± 0.69	0.70
Total IgE, IU/mL	54.42 ± 7.15	234.01 ± 47.38	<0.0001
Anti-TG, IU/mL	8.57 ± 0.82	18.38 ± 3.56	0.009
Anti-TPO, U/mL	14.80 ± 0.79	82.65 ± 23.45	0.005

Data were expressed as mean ± standard error of the mean. Abbreviations: PTX3: pentraxin 3, CRP: C-reactive protein, LYM: lymphocyte, NEU: neutrophil, BAS: basophil, EOS: eosinophil, PLT: platelet, ALT: alanine aminotransferase, AST: aspartate aminotransferase, Anti-TPO: Anti- antithyroid peroxidase, Anti-TG: Anti- thyroglobulin. P-values less than 0.05 were considered significant and displayed in bold.

correlation between D-dimer and PLT levels ($r = -0.213$, $p = 0.034$). However, no correlation was observed between plasma PTX3 levels and other parameters, such as total IgE, Anti-TPO, Anti-TG, D-dimer, and transaminase levels, lymphocyte, neutrophil, basophil, and eosinophil cell counts, UAS7 scores, or disease duration. We also performed a multivariable stepwise regression analysis to estimate the effects of various clinical parameters on PTX3 levels in CSU patients. The variables of CRP, D-dimer, ALT, AST, total IgE, Anti-TPO, Anti-TG, PLT, and disease activity were added to the model in a stepwise manner. The final model showed that the CRP levels significantly affected PTX3 levels such that one unit increase in the CRP level increased to 38.19 units in the PTX3 level (95% confidence interval [17.40-58.98], $p < 0.001$). These findings indicate that circulating PTX3 and CRP levels are strongly related and elevated in CSU patients.

Discussion

We investigated plasma PTX3 levels and several other clinical parameters in CSU patients. This is the first study with the largest series of CSU patients, proving that circulating PTX3 and CRP levels are positively correlated and significantly increased in CSU patients compared to healthy controls. We also found that PTX3 levels were elevated with increasing CSU severity. These findings suggest that high plasma levels of PTX3 in patients with CSU can be utilized as an indicator of the inflammatory state.

PTX3 deficiency, in an experimental asthma model, resulted in increased airway hyperresponsiveness, mucus production, and IL-17A-predominant inflammation, suggesting that PTX3 plays a regulatory role in allergic inflammation.²¹ In addition to TNF- α , a pro-inflammatory cytokine released by mast cells during allergic inflammation and found in the urticarial lesion site, IL-17, which plays a role in the pathogenesis of many autoinflammatory diseases, was found to be high in CSU patients and showed a positive

correlation with UAS7 scores.^{5,22,23} PTX3 expression can be induced by various inflammatory mediators, such as IL-1 β , TNF- α , and IL-17.¹⁵ This may account for high circulating PTX3 levels detected in CSU patients. In addition, no study has yet been conducted regarding PTX3 concentrations in skin punch biopsy materials in such patients. This may provide further insight into local and systemic regulation of PTX3 in CSU. In asthma with airway infiltration by inflammatory cells in the pathophysiology, PTX3 levels were high in the sputum of non-eosinophilic asthma patients.²⁴ The production of PTX3 in the local inflammation site, unlike CRP, which is synthesized in the liver, may explain its high levels in the sputum of asthmatic patients and low levels in the peripheral circulation. In a study evaluating PTX3, D-dimer, and eosinophil levels in children with allergic asthma, all markers were elevated compared to healthy controls. Still, no correlation was found with lung functions, asthma control grade, asthma severity, eosinophil count, or D-dimer level.²⁵ Similarly, our study found that CSU patients had increased CRP, D-dimer, and lymphocyte levels. Still, except for CRP, there was no correlation between PTX3 and other laboratory markers, disease severity, urticaria activity score, or other disease parameters.

Moreover, in an experimental model of food allergy, it was shown that shrimp-allergic mice had increased total IgE levels and PTX3 levels in serum and small intestinal compared to control mice, implying PTX3 as an underlying cause of mast cell degranulation and allergic inflammation.¹⁹ This may also account for the high PTX3 and total IgE levels we found in patients with CSU, a mast cell-derived disease.

Serum CRP levels, a useful predictor of inflammation, are known to be elevated in CSU patients.^{12,13,26,27} Recently, following various clinical studies, it has been suggested that high levels of CRP and its strong correlation with other inflammatory markers and disease activity can be utilized as a biomarker of CSU activity and response to treatment, particularly since high CRP levels may predict a poor response to antihistamines and a good response to

cyclosporine.^{6,12,13,28,29} As expected, we found serum CRP levels higher in the patient group and elevated with the disease severity. We also observed a strong association between CRP and PTX3 concentrations in CSU patients. There was also a positive correlation between CRP and D-dimer levels in our patients, consistent with previous findings.³⁰ However, unlike previous studies, we found neither a correlation between UAS7 and CRP nor a significant difference in CRP levels between the antihistamine-resistant and antihistamine-responsive groups.^{27,30} In one study, the authors reported a positive association between higher platelet count and serum CRP levels in CSU patients with more severe disease activity.³¹ However, our study did not observe a significant difference in PLT numbers between the patient and control groups and any correlation between PLT and CRP, PTX3, or disease activity in CSU patients. Finally, circulating D-dimer levels were elevated and positively correlated with UAS7 and CRP levels and disease activity in our patients, consistent with the previous reports,³²⁻³⁶ further supporting the involvement of the coagulation cascade in CSU pathogenesis.

In conclusion, circulating levels of CRP and PTX3, two members of the pentraxin family, are significantly correlated and elevated with the severity of disease in CSU patients, indicating their utility as inflammatory markers in CSU. PTX3 is mainly produced at sites of inflammation by different cell types, particularly endothelial cells, macrophages, and neutrophils,^{10,14,15} yet the cellular sources of plasma PTX3 remain largely unexplored. In-depth mechanistic studies will be needed to elucidate the impact of PTX3 dysregulation in CSU pathogenesis. The main limitation of this study is the relatively small number of patients and controls, so more comprehensive studies assessing PTX3 levels in the blood and skin biopsy samples in more significant numbers of patients and healthy individuals are needed. In addition, the failure to measure the PTX3 levels of the patients after treatment and to evaluate the success of this marker in predicting the response to treatment is another limitation of the study and should be determined in future studies.

Conflict of Interest

The authors declare no conflict of interest.

Statement of Ethics

This study was conducted by the World Medical Association Declaration of Helsinki and approved by the İhsan Doğramacı Bilkent University Human Research Ethics Committee (#2022_12_03_01). Written informed consent was collected from all individual participants in this study.

Author Contributions

Şengül Beyaz, Serkan Belkaya, and Nida Öztop have made substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data;

have been involved in drafting the manuscript or revising it critically for important intellectual content.

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