

Acute-phase response and its biomarkers in acute and chronic urticaria

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Abstract

Introduction: Since urticaria is a persisting inflammatory disease it is important to establish the prognostic factors for the duration and severity of the disease.

Aim: To evaluate serum concentrations of selected acute-phase proteins (APP) in patients with various forms of urticaria as compared to healthy volunteers and also to analyze these concentrations in different types of urticaria. Additionally, to evaluate the correlation between serum levels of selected APP and disease activity.

Material and methods: Serum concentrations of C-reactive protein (CRP), α_1 -acid glycoprotein (AGP), α_1 -antichymotrypsin (ACT), α_1 -antitrypsin (AT), ceruloplasmin (Cp), transferrin (Tf), α_2 -macroglobulin (α_2 M) and haptoglobin (Hp) were measured. Quantitative measurement was conducted using the rocket immunoelectrophoresis. Disease activity was assessed with the use of total symptom score.

Results: Analysis of serum APP concentrations revealed statistically higher serum concentrations of CRP, AGP and ACT in the entire group of patients with urticaria in comparison with the control group. In the entire group of patients with urticaria, CRP, AGP, ACT, Cp and Hp correlated positively with disease activity, intensity of pruritus and the number and size of urticarial wheals. Statistically lower serum concentrations of CRP, ACT, Cp and Hp were detected in the group of patients with acute urticaria (AU) and angioedema together, compared to the patients suffering from AU only.

Conclusions: Patients with symptoms of various forms of urticaria present a distinct profile of serum APP concentrations. A significant correlation observed between CRP, AGP, ACT, Cp, Hp and clinical activity score points to the potential role of APP as markers of the urticarial activity.

Key words: chronic urticaria, acute phase reaction, proteins.

Introduction

Urticaria is a disease characterized by the development of wheals, angioedema, or both of these features. The spectrum of clinical manifestations of different urticaria subtypes is very wide and it is observed that two or more different subtypes of urticaria can coexist in 1 patient. According to the latest EAACI/GA2LEN/EDF/WAO [1] guideline, acute urticaria (AU) is defined as the occurrence of spontaneous wheals, angioedema, or both for less than 6 weeks. Chronic urticaria (CU) subtypes include chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CINDU). Acute-phase response (APR) is an early, nonspecific but very complex reaction of the organism following infections, inflammatory processes, tissue injuries, tumor growth induced for the maintenance or restoration of homeostasis [2–4].

Clinically APR exerts multidirectional effects on both humoral and cellular types of immunity as well as on many metabolic processes [5, 6]. Many cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) are considered as the main stimulators of APR [7, 8]. Biochemically APR is characterized by changes in serum concentrations of different circulating proteins (acute phase proteins – APP). Serum concentrations of the most of APP rise by 25%, whereas serum concentrations of transferrin (Tf) and α_2 -glycoprotein (AGP) decrease by 30% during APR. Some of the circulating APP (e.g. α_2 -macroglobulin – α_2 M) change insignificantly during APR. The concentration of selected circulating proteins may rise by 50% (e.g. ceruloplasmin – Cp). In case of α_1 -antichymotrypsin

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(ACT), α_2 -glycoprotein (AGP), haptoglobin (Hp) and α_1 -antitrypsin (AT), a two- or threefold increase in the serum concentration is observed. The serum concentration of C-reactive protein (CRP) or serum amyloid A (SAA) increases even 1000 times during APR [7, 8].

Recent studies revealed that CU is a persisting inflammatory disorder of the skin characterized by mast cell degranulation and perivascular infiltrations composed mainly of CD4+ lymphocytes, monocytes, neutrophils, eosinophils and basophils [2, 7]. The association of changes in serum concentrations of APP with the severity of inflammation indicates that selected APP may be useful in diagnosing and monitoring the activity and management of different diseases. Since CU is a persisting inflammatory disease and due to its often idiopathic background, it is important to establish the prognostic factors for the duration and severity of the disease. Identification of the severity biomarkers will allow selection of patients with a resistant and refractory course of CU in whom alternative therapies to antihistamines should be used.

Aim

The aim of the study was to evaluate serum concentrations of selected APP and their glycosylation profile in patients suffering from various forms of urticaria as compared to the control group (healthy volunteers). Comparison of APP serum concentrations between different types of urticaria was also performed. The additional aim was the evaluation of the correlation between serum levels of selected APP and urticaria activity, as well as biochemical findings performed as a diagnostic regimen of urticaria.

Material and methods

One hundred and three patients were included in the study: 15 subjects suffering from AU and 88 subjects suffering from CU. All the patients were treated in the Department of Dermatology, Poznan University of Medical Sciences.

Among 103 patients selected, there were 80 women and 23 men, aged 13 to 79 (mean age: 40 years). The control group comprised only 20 individuals (13 women and 7 men, aged 18 to 41, mean age: 30 years) because of the problem with enrolling of healthy volunteers with a negative history of urticaria and angioedema. The researchers were aware that all conclusions based on the results of the study should be drawn with caution because of the disproportion between the study and control group.

All the patients underwent the following diagnostic tests: full blood count with peripheral blood count, erythrocyte sedimentation rate, urine analysis, serum glucose, hepatic enzymes and creatinine level, antistreptolysin O titer. In addition, stool examination for parasites, serology tests for toxoplasmosis and toxocarosis, thyroid gland's hormones level (thyroid stimulating hormone –

TSH, and free thyroxine – fT4), chest X-ray and abdominal ultrasonography were performed. Moreover, patients were consulted by the dentist and ENT specialist. Such screening for patients with urticaria was needed in order to eliminate patients in whom the elevated concentration of inflammatory mediators might have resulted from other reasons than urticaria, e.g. hidden foci of infection.

In each patient, a detailed case history was taken considering the duration of symptoms, activity of urticaria, concomitant angioedema, family history, concomitant diseases and treatment. According to the collected data, several groups of patients with urticaria were distinguished. Patients suffering from urticaria for up to 6 weeks were classified as the acute type of urticaria (15 patients). Patients with symptoms of AU during examination received standard treatment (e.g. dexamethasone *i.v.*, clemastine *i.v.*). Patients in whom symptoms lasted for more than 6 weeks were classified as the chronic type of urticaria (88 patients). Patients suffering from CU were recommended to discontinue the anti-histaminic drug 7 days before the following provocative testing: autologous serum skin test (ASST), oral provocation with aspirin, intradermal test with penicillin, provocative test with heat, cold and pressure, and exercise trial. In order to estimate acute phase reaction biomarkers in the serum of patients with various types of urticaria, patients were classified into one of the following types of CU: spontaneous (42 patients), autoimmune (19 patients), inducible (17 patients), aspirin-exacerbated (10 patients) according to the results of the diagnostic procedures.

Intradermal ASST was performed according to the method described by Sabroe *et al.* [9]. Serum-induced wheal greater than 1.5 mm than control (physiological saline) was regarded as positive. A provocative test with aspirin as well as provocation with physical factors were performed according to the protocol used in the Dermatology Department of Poznan University of Medical Sciences.

Urticaria activity was assessed with the use of TSS scale (total symptom score) as described by Lorette *et al.* [10]. TTS was calculated in relation to the number and size of wheals and intensity of pruritus. The biggest diameter of a single wheal was estimated according to the following scheme: 0 = 0 cm, 1 = wheals' diameter < 1.5 cm, 2 = wheals' diameter > 1.5 cm and 3 = wheals' diameter > 2.5 cm. The number of wheals was calculated as follows: 0 = no wheals, 1 = the number of wheals < 10, 2 = the number of wheals > 10, 3 = numerous wheals affecting the whole skin. The pruritus intensity was measured according to the following pattern: 0 means no pruritus, 1 = mild pruritus, 2 = severe itch not interfering with daily activity, 3 = very intense itch interfering with daily activity. The TSS score in the studied group was between 2 and 9.

All blood samples were collected during eruption of urticarial wheals (in the active phase of disease) by antecubital puncture. The samples were centrifuged and stored at -20°C .

Table 1. The number of patients and mean age of patients in studied groups

Parameter	Number of subjects	Female : male ratio	Mean age [years]	Min. age	Max. age
Chronic urticaria:	88	67 : 21	40.4 ±17.2	13	79
Aspirin-exacerbated	10	7 : 3	38.8 ±18.3	13	76
Inducible	17	11 : 6	29.2 ±14.5	14	63
Autoimmune	19	15 : 4	48.9 ±15.9	18	76
Spontaneous	42	34 : 8	41.5 ±16.2	17	79
Acute urticaria	15	13 : 2	38.7 ±17.1	14	79
Control group	20	13 : 7	30.95 ±6.4	18	41

Serum concentrations of APP were measured in all patients from the studied group as well as in healthy volunteers. The assessed APP were as follows: CRP, AGP, ACT, AT, Cp, Tf, α_2 M, Hp. Quantitative measurement was conducted with the rocket immunoelectrophoresis by Laurell [11]. The evaluation of glycosylation profiles and reactivity coefficients (RC) for AGP (AGP-RC) and ACT (ACT-RC) were done by means of the cross immunoelectrophoresis affinity by Bog-Hansen with concavalin A (Con A) as a ligand [11].

Serum concentrations of APP and their glycosylation profiles were measured in the Department of Biology and Environmental Protection of Poznan University of Medical Sciences.

Statistical analysis

The Kruskal-Wallis variance analysis was used to analyze the differences in serum concentrations of APP and their glycosylation profiles between the studied groups of patients. The Mann-Whitney *U*-test was used to compare serum concentrations of APP between the studied groups of patients and healthy volunteers, between groups of patients suffering from particular types of urticaria, as well as between serum concentrations of APP and urticaria intensity in studied groups of patients. The Spearman correlation rank test was used to assess correlations between serum concentrations of APP and

TSS as well as between serum concentrations of APP and selected laboratory parameters.

Results

Among the 103 patients suffering from particular types of urticaria there were 80 (78%) women and 23 (22%) men. The group of healthy volunteers comprised of 13 (65%) women and 7 (35%) men. The number of patients and the mean age of patients in studied groups are presented in Table 1.

Among the patients with CU, the aspirin-exacerbated type comprised 11.4%, inducible type – 19.3%, autoimmune type – 21.6%, whereas spontaneous urticaria comprised 47.7%. The mean duration of symptoms in patients suffering from AU was 7 days. In most patients with AU (in 8 out of 15 persons; 53.3%) symptoms subsided within 1 or 2 days. The mean duration of the disease in patients suffering from CU was 28.9 months (min. 2 months, max. > 10 years). The majority of patients in the CU group had episodes of urticarial wheals for 6 months, whereas 5 patients experienced urticaria for more than 10 years.

Forty-one (39.8%) subjects in the entire study group (*n* = 103) experienced episodes of angioedema associated with urticarial wheals. Eight (53.3%) patients with AU (*n* = 15) had simultaneous episodes of urticaria and angioedema, while in patients with CU (*n* = 88), only 33 (37.5%) patients presented symptoms of angioedema.

Analysis of serum APP concentrations and their glycosylation profiles revealed statistically higher (*p* < 0.05) serum concentrations of CRP, AGP and ACT in the entire group of patients suffering from urticaria (acute and chronic type together, *n* = 103) in comparison with the control group. Statistically higher values of AGP-RC were identified in the serum of the whole group of all subjects with urticaria (*n* = 103) in comparison with healthy volunteers (*n* = 20) (*p* < 0.05).

In turn, there were statistically higher serum concentrations of CRP, AGP, ACT, Cp and Hp in patients with AU (*n* = 15) in comparison with healthy volunteers (*p* < 0.05) (Figure 1).

Patients suffering from CU presented statistically higher serum concentrations of CRP, ACT and Hp vs. the control group (*p* < 0.05).

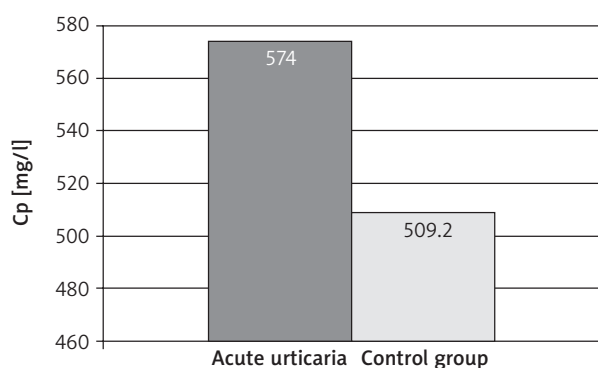


Figure 1. Statistically higher mean serum concentrations of Cp in the group of patients with AU (*n* = 15) comparing with the control group (*p* < 0.05)

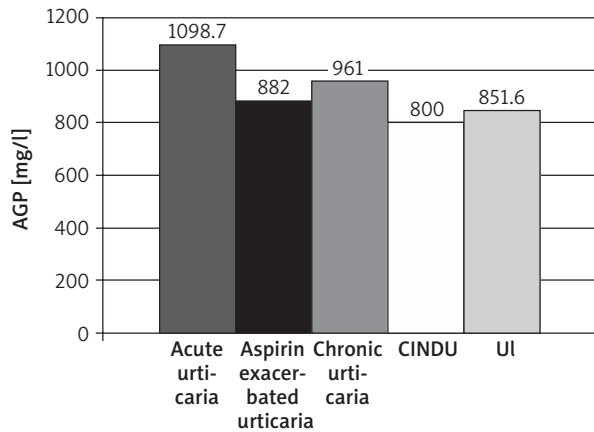


Figure 2. The mean serum concentrations of AGP in different types of urticaria. Statistically higher serum concentrations of AGP in AU than in CINDU

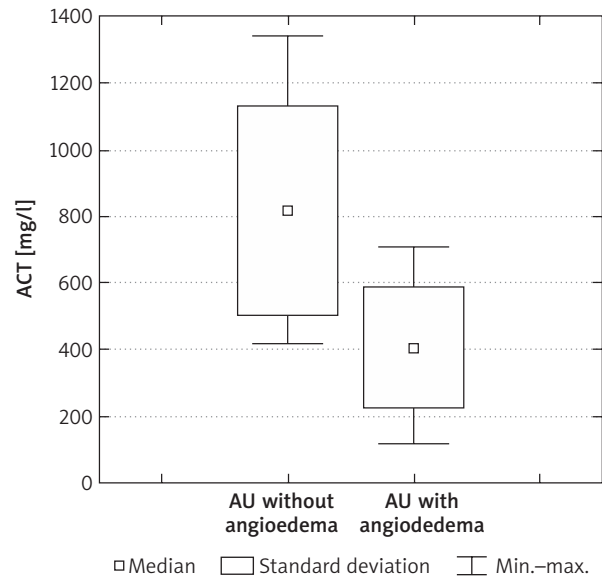


Figure 3. Statistically lower serum concentrations of ACT in the group of patients with AU and angioedema comparing to the group of patients with AU only ($p = 0.006$)

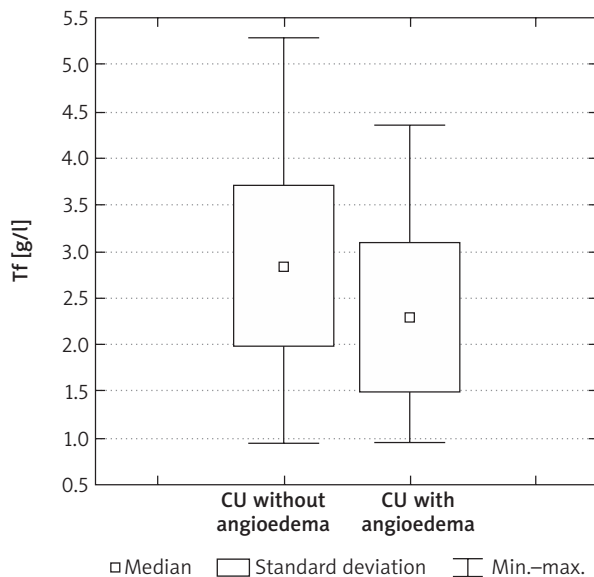


Figure 4. Statistically lower serum concentrations of Tf in the group of patients with CU and angioedema comparing to the group of patients with CU only ($p < 0.05$)

Statistically higher serum concentrations of CRP, AGP, ACT and Hp were also detected in the group of patients with CSU comparing to healthy volunteers ($p < 0.05$). The mean serum concentration of CRP was statistically higher in patients suffering from the autoimmune type of urticaria ($n = 19$) in comparison with the control group ($p < 0.05$). In turn, circulating Tf was statistically lower in autoimmune urticaria vs healthy subjects.

The study also revealed statistically higher serum concentrations of CRP and Hp in patients with CINDU comparing to healthy volunteers ($p < 0.05$).

In addition, we detected higher serum concentrations of CRP and ACT in the group of patients suffering from

aspirin-exacerbated urticaria in comparison with the control group ($p < 0.05$).

Analysis of serum concentrations of APP in subjects with different types of urticaria revealed statistically higher values of AGP and ACT in AU comparing to CINDU ($p = 0.023$ and $p = 0.026$ respectively) and statistically higher values of CRP in AU vs the autoimmune type ($p = 0.031$) (Figure 2).

Statistically lower serum concentrations of CRP, ACT, Cp and Hp were detected in the group of patients suffering from AU and angioedema together, compared to the patients suffering from AU only ($p = 0.006$; $p = 0.006$; $p = 0.02$; $p = 0.02$, respectively) (Figure 3). In the group of patients suffering from CU associated with angioedema, serum concentrations of Tf were statistically lower ($p < 0.05$) than in the group of patients without angioedema (Figure 4).

In the entire group of patients with urticaria ($n = 103$) CRP, AGP, ACT, Cp and Hp correlated positively with disease activity (measured by TSS), intensity of pruritus and the number and size of urticarial wheals (Figure 5).

In patients with AU ($n = 15$), serum concentrations of Tf ($r = 0.762$; $p = 0.001$), α_2M ($r = 0.743$; $p = 0.001$) and AT ($r = 0.631$; $p = 0.01$) correlated positively with the duration of the disease, whereas in patients with CU, the duration of symptoms correlated negatively only with the serum concentration of ACT ($r = -0.214$; $p = 0.04$) (Figure 6).

Discussion

Contrary to the unified clinical picture, etiopathogenesis of particular types of urticaria has not been fully

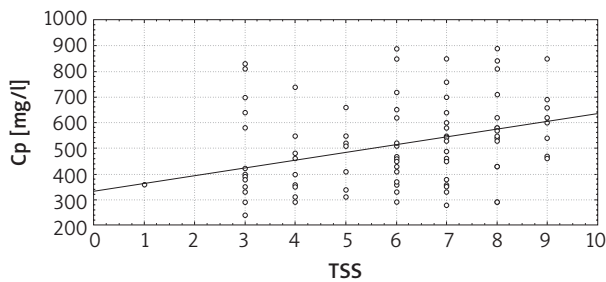


Figure 5. Statistically significant correlation between the serum concentration of Cp and the TSS in patients with urticaria (acute and chronic type together)

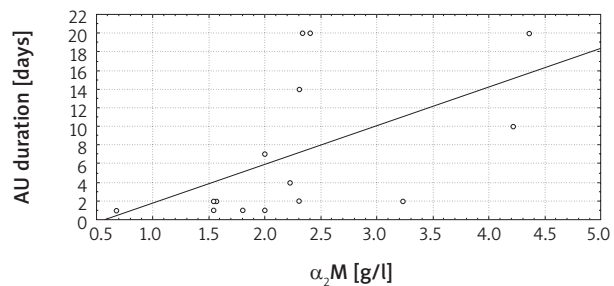


Figure 6. Statistically significant correlation between the serum concentration of α_2M and the duration of disease in patients with AU

explained. The new data point to a significant role of inflammatory processes in the development of the disease. The theory of allergic inflammation explains immunological processes in IgE-mediated diseases such as allergic asthma, atopic dermatitis, allergic rhinitis and AU [8]. Mechanisms that lead to the histamine release are multifactorial including allergic and inflammatory reactions. Mast cells are the source of many pro-inflammatory cytokines such as TNF- α , IL-4, IL-5, IL-1, IL-3, IL-8, IL-10, IL-13, GM-CSF, MIP-1 α , MIP-2 α [8, 12–15]. Therefore, mast cells are not only effector cells in allergic reactions, but may also regulate the intensity of these processes [12]. Histamine is one of the mediators of APR and regulates synthesis and secretion of cytokines responsible for the late phase of IgE-mediated allergic inflammation [13, 16]. Thus, histamine may influence secretion of specific APP in different types of urticaria. According to the recent findings, the pattern of cytokines and APR biomarkers seems to be specific of particular types of urticaria [17–19].

In all types of CU, regardless of the cause, serum concentrations of CRP, ACT and Hp were statistically higher than in the control group. In patients with AU, serum concentrations of CRP, AGP, ACT, Cp and Hp were statistically higher comparing with healthy volunteers. There were no statistically significant differences in serum concentrations between patients suffering from different types of urticaria and the control group regarding remaining APP measured during the study. These findings suggest that mediators of APR may contribute to development of urticarial symptoms and enhance urticarial inflammation. However, the conclusions should be drawn with caution because of the lack of proportion between the study and the control group.

We also found elevated serum concentrations of different APR biomarkers in all studied types of CU (aspirin-exacerbated, CSU, autoimmune, CINDU) creating a different pattern of APR biomarkers specific of a particular type of urticaria. This leads to the conclusion that distinct mechanisms are responsible for the same clinical picture in all types of the disease. Among all of analyzed APP, only the serum concentration of CRP was increased in all types of urticaria comparing to the control group.

This is in agreement with results of other studies [17, 18, 20]. In turn, elevated levels of Cp were observed only in patients with AU comparing to healthy volunteers indicating that Cp is a specific biomarker of AU. Cp plays an important role in histamine metabolism and regulates its serum concentration [21]. Releasing of histamine in AU is usually IgE-mediated and results in augmentation of Cp synthesis [21].

The patients with autoimmune urticaria comprised the only studied group with serum concentrations of Tf statistically lower comparing to the control group. Autoantibodies engaged in the pathogenesis of autoimmune urticaria are directed against α -fragment of a high affinity receptor for IgE (Fc ϵ RI) or against IgE molecule and belong to the class of IgG (IgG1, IgG3). Interaction of anti-IgE antibodies with IgE molecules bound to Fc ϵ RI receptors has multidirectional effects such as degranulation of mast cells or suppression of IgE synthesis by lymphocytes B [12]. In turn, Tf stimulates lymphocytes T to produce IgE. A decreased level of Tf may be involved in pathogenesis of autoimmune urticaria due to its involvement in IgE synthesis and anti-IgE – Fc ϵ RI interaction.

In the group of patients suffering from aspirin-exacerbated urticaria, we found statistically higher serum concentrations of CRP and ACT comparing to the control group. Similar results were also obtained by other authors who found statistically increased levels of CRP in patients with non-steroidal anti-inflammatory drugs (NSAIDs)-induced AU as compared with healthy subjects [19]. The mechanism of this disorder is based on inhibition of cyclooxygenase-1 (COX-1) and formation of leukotrienes that may act as additional proinflammatory agents enhancing APR. The ACT acts as an inhibitor of proteases including chymotrypsin released by mast cells [12]. Increased release of proteases from mast cells infiltrating the human skin may result in an increased serum concentration of ACT in patients suffering from aspirin intolerance in urticaria. ACT is responsible for reducing degranulation of mast cells after allergen stimulation. It influences antigen presentation by Langerhans cells and modulates lymphocytes activity [22–27]. According to these data, an increased serum concentration of ACT

may lead to limitation of urticarial symptoms. According to some authors, the imbalance between proteases synthesis and their inhibitors is responsible for inducing or developing symptoms of many different diseases [28, 29].

There are some reports suggesting that protease inhibitor deficiency, mainly AT, is responsible for developing urticaria. The study conducted by Doeglas and Bleumink on 92 cases of CU revealed a statistically lower serum concentration of AT in patients with cold urticaria and in urticaria associated with angioedema [30]. The same authors examined 281 patients and demonstrated that CU is characterized by a lower serum concentration of AT comparing to healthy subjects. It led to the conclusion that a lower serum concentration of AT may predispose to developing certain types of CU [31]. This is in agreement with the results of Imai study according to which a lower serum concentration of AT was characteristic of patients with spontaneous urticaria [32]. There are also some studies reporting statistically lower serum concentrations of AT in patients with cholinergic urticaria [33]. Probably increased activity of protease inhibitors inactivating proteases released from mast cell leads to a decrease in their concentrations in patients with urticaria [32]. However in our study we did not find any statistically differences in the serum concentration of AT between patients with different types of urticaria and the control group. Similarly, Chodirker *et al.* did not find any significant decrease in the AT level within the group of patients suffering from spontaneous or cold-induced urticaria vs the control group [34].

We also detected a statistically higher serum level of Hp in patients with CINDU comparing to the control group. Ping *et al.* described an increased expression of Hp mRNA in the skin of patients with certain inflammatory dermatoses such as psoriasis, lichen planus vs. healthy skin. On the contrary, autoimmune skin disorders like lupus erythematosus, pemphigus or pemphigoid were characterized by a significantly decreased expression of Hp mRNA vs. healthy skin [35]. Hp modulates the functions of the immune system, it acts mainly on Langerhans and mast cells and may be engaged in pathogenesis of urticaria.

A moderate increase in the CRP level (3–10 mg/l) is correlated with a higher risk of cardio-vascular disease, metabolic syndrome and colon carcinoma [36]. Similar findings are also described for myocardial infarction, graft vs. host reaction, vessels disease, and rheumatoid arthritis [37]. Lin also observed increased CRP serum concentrations in 11 analyzed cases of CU [38]. C-reactive protein is considered to be a sensitive marker of inflammation [27], which according to Lin's study correlates with the concentration of IL-6 in serum of the healthy population, as well as in the study group [39]. Du Clos suggested a protective role of CRP in the immune system. It acts as an inhibitor of autoimmune reactions, due to binding of nuclear antibodies [37]. Insufficiency of

CRP may also promote development of lupus erythematosus [36]. This phenomenon can be an explanation for the decreased level of CRP in a group of patients with autoimmune comparing to AU. The biggest difference in CRP concentration was observed in acute vs. chronic autoimmune urticaria (statistically significant difference). Piconi *et al.* proved that production of proinflammatory cytokines such as TNF- α is higher in the group of patients with CSU presenting a negative autologous serum skin test, than in patients with autoimmune urticaria (positive ASST) in whom intensity of the inflammatory process is much more lower [40]. This is in agreement with our observations and may be caused by the presence of the hypothetical factor inhibiting production of cytokines by peripheral blood mononuclear cells (PBMCs) [40].

Patterns of APR biomarkers in the serum of patients suffering from acute and CSU were similar in the analyzed material. However AU was characterized by the highest serum concentration of CRP comparing to other types of urticaria. Acute urticaria is mainly IgE mediated and histamine influences the secretion of many different cytokines engaged in development and maintenance of inflammation [16]. Lin *et al.* suggested that the increased concentration of CRP as well as other proinflammatory cytokines may be characteristic of the late phase of type I hypersensitivity reaction [38].

We only observed statistically higher serum concentrations of AGP-RC while analyzing the whole group of patients with urticaria regardless of the type of the disease in comparison to healthy volunteers. There were no statistically significant differences in serum concentrations of APP reactivity coefficients while analyzing the particular types of urticaria separately. In turn, a statistically higher serum concentration of AGP comparing to the control group was detected in patients with AU and CSU. The serum concentration of AGP was also statistically higher in AU than in CINDU. α_2 -acid glycoprotein has multifactorial effects on the immunological system inhibiting activity of many cells such as neutrophils, monocytes or macrophages thus suppressing the inflammation.

Analysis of differences in serum concentrations of APR biomarkers and selected clinical features revealed higher levels of CRP in the group of patients suffering from AU associated with angioedema than in the group of patients without angioedema. Lin *et al.* observed a negative correlation between serum concentrations of CRP and histamine in IgE-mediated reactions [39]. There were also statistically lower serum concentrations of ACT, Cp and Hp in patients with AU with angioedema comparing to patients without angioedema. To conclude, the changes in circulating APP are dependent on the extension of the local inflammatory response but demonstrate no relation to the causative factor. In urticaria associated with angioedema where inflammatory reactions are localized within a deeper layer of the skin and/or subcuta-

neous tissues, the serum concentrations of selected APP are lower than in patients with the disease of a milder course (without angioedema). This is probably due to the fact that certain APP suppress the inflammatory reactions thus their deficiency may promote development of a wider spectrum of clinical symptoms.

It has been proved that serum concentrations of certain APP such as CRP and IL-6 are higher in severe CU than in patients presenting milder symptoms of the disease [7, 20]. We also observed positive correlations between serum concentrations of the most studied APP and disease activity measured with TSS. Higher serum levels of CRP, AGP, ACT, Cp and Hp were characteristic of the patients with a more severe course of the urticaria (higher TSS). Patients with a higher serum level of aforementioned APR biomarkers presented more intense itch, a higher number and size of urticarial wheals. Similarly, in the group of patients with the acute type of urticaria, a more severe course of the disease was associated with increased serum levels of CRP, ACT and Cp as well as decreased levels of RC-AGP. C-reactive protein acts as a potent activator of the complement cascade and coagulation/fibrinolysis processes. Its elevated level contributes to a significant increase in the cardiovascular risk and may induce or enhance inflammatory response [41].

We also observed that patients with AU presented a more prolonged disease course and had statistically a higher serum concentration of Tf, α_2 M and AT. There was also a positive correlation between duration of the symptoms and the serum level of Tf, α_2 M and AT in the group of patients suffering from AU. This leads to a conclusion that both activity and duration of the disease depend on the intensity of inflammatory processes and they are expressed by a specific pattern of APR biomarkers. Urticaria is usually a long-term disease characterized by an unpredictable course. Therefore, it is important to define the prognostic factors that allow to predict the duration and severity of the disease. The results of this study point to some APP such as Tf, α_2 M, AT or ACT as good biomarkers of urticaria severity [19].

Until now, elevated serum concentrations of APP have been described in patients suffering from spontaneous CU, AU and delayed pressure urticaria [18–20]. Results of our study revealed increased concentrations of APP also in autoimmune (CRP, Tf) and inducible (CRP, Hp) types of urticaria. Collected data proved that acute and certain types of CU present specific changes in APP serum concentrations and their glycosylation profiles. Whether the increase of circulating APR biomarkers is only an epiphenomenon or are they actually engaged in pathogenesis of urticaria and enhance the inflammation, still requires further studies. However, characterization of a specific profile of APP provides information about the type and activity of the disease. A significant correlation observed between CRP, AGP, ACT, Cp, Hp and clinical activity score of urticaria (TSS) points to the potential role

of APP as markers of the urticarial activity. Estimation of APR biomarkers serum levels may be a useful tool in diagnosing and monitoring activity and response to treatment of urticaria.

Despite the limitations of the study such as disproportion between the study and the control group, some conclusions may be drawn with caution. A significant correlation observed between the acute-phase proteins concentration in the serum and clinical activity score of urticaria points to the potential role of these proteins as markers of the disease activity. Estimation of acute phase reaction biomarkers levels in the serum may serve as a useful tool in diagnosing and monitoring the activity of urticaria and its response to treatment.

Conflict of interest

The authors declare no conflict of interest.

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