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Systemic inflammatory response and calcification markers in patients with long lasting moderate-severe chronic spontaneous urticaria

Background: Low grade inflammation is associated with both chronic spontaneous urticaria (CSU) and atherosclerosis. Data regarding an association between urticarial inflammation and atherosclerosis and subsequent cardiovascular events are scarce. It has been demonstrated that matrix GLA protein (MGP), a biomarker of arterial calcification, is increased in patients with atherosclerosis. **Objectives:** To evaluate circulating levels of markers of arterial calcification and acute phase response (APR) in patients with CSU. **Methods:** Concentrations of MGP and IL-6 were measured in venous blood samples of patients with long-lasting moderate-severe CSU. **Results:** There were no significant differences in serum MGP concentration between healthy subjects and CU patients. Serum IL-6 concentration was significantly higher in CSU patients as compared with healthy subjects. **Conclusions:** The results confirm that CSU is accompanied by a low grade systemic inflammatory state. However, the long lasting urticarial inflammation was not paralleled by an increased circulating level of the calcification marker matrix Gla protein.

Key words: matrix Gla Protein, chronic spontaneous urticaria, acute phase response, calcification, chronic inflammation

Chronic spontaneous urticaria (CSU) is characterised by a non-specific local inflammatory process accompanied by a systemic acute phase response (APR) [1-3]. It has been demonstrated that inflammatory markers associated with APR, such as CRP, IL-6 and matrix metalloproteinase 9 (MMP-9) correlate with the severity/activity of CSU [1-6].

Interestingly, CSU patients have also been shown to have a significantly higher prevalence of metabolic syndrome compared with age-matched controls [7]. In addition, the possible associations between the progression of urticaria and metabolic syndrome may promote systemic inflammation in CSU patients [7]. It has been indicated that both circulating levels of APR markers and the presence of metabolic syndrome are associated with atherosclerosis and an increased risk of cardiovascular events. Atherosclerosis is a multi-factorial disease with an important contribution of vascular calcification characteristic for both early and late stages of the disease. Vascular atherosclerotic calcification is easily detectable with imaging techniques and correlates well with cardiovascular events. Vascular calcification is present in different chronic inflammatory diseases [8-10]. Matrix Gla protein (MGP) is an inhibitor of calcification *in vivo* and it is upregulated in atherosclerotic lesions [10]. It has been indicated that circulating MGP may serve as a biomarker of atherosclerotic calcification [11, 12].

Biomarkers are very useful tools in clinical practice for better diagnostic and therapeutic decisions. However, biomarkers to monitor the progression of CSU are poorly recognised. Therefore, the aim of the present study was to

investigate serum concentration of MGP and its association with low grade inflammation in patients with long-lasting, moderate-severe CSU.

Materials and methods

Seventeen non-smoking patients with active, poorly controlled CSU (15 women and 2 men; mean age: 42 years; range: 29-45 yr.), without apparent concomitant cardiovascular disease, were enrolled in the study. The disease had lasted for more than four years (mean duration: 6 years, range: 4.5-10 years), without spontaneous remission.

Urticaria activity score (UAS) was estimated over four days and on the day of blood sampling. The study comprised CU patients with moderate-severe urticaria symptoms as per the four days UAS (moderate (9-16) and severe (17-24), respectively). None of the subjects had taken oral corticosteroids within 2 months or antihistamines within at least 4 days before the study. Each patient underwent the following investigations: routine laboratory tests (full blood count, urine analysis, ESR, C-reactive protein, serum glucose, hepatic functions and creatinine), immunoglobulins and complement in serum/plasma, stool (for parasites), hepatitis serology (anti-HCV, HBsAg), antinuclear and antithyroid microsomal antibodies, thyroid function and *H. pylori* tests, and abdominal ultrasonography.

In addition, the result of the autologous serum skin test (ASST) was negative. The control group consisted of 16

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sex-, age- BMI (<30) matched healthy subjects. The Ethics Committee of the Medical University of Silesia approved the study.

Serum MGP concentration was measured using ELISA (Biomedica Medizinprodukte, Vienna-Austria) with lower detection limit of 0.3 nmol/L. Concentration of IL-6 in serum was measured by ELISA (Endogen, Inc., Woburn-USA). The Mann-Whitney *U* test was used to compare data between the groups. The correlation coefficient was obtained by Spearman test. *P* values lower than 0.05 were considered significant.

Results

No significant differences were observed in serum MGP concentration between the healthy subjects and the CU patients (median and interquartile ranges: 3.81 (3.56-5.42) and 4.17 (2.8-5.7) nmol/L, $p>0.05$) (figure 1). Serum IL-6 concentration was significantly higher in CSU patients as compared with the healthy subjects (median and interquartile ranges: 11.64 (10.34-11.93) and 4.95 (4.05-5.7) pg/mL, $p<0.0001$). No significant correlations were found between concentrations of IL-6 and MGP ($r = 0.39$, $p = 0.12$) nor between MGP and UAS ($r = 0.04$, $p = 0.88$) in CSU patients. It has been suggested that patients with severe and uncontrolled CSU should be evaluated for metabolic syndrome in order to reduce cardiovascular risk and improve CSU outcomes [7].

Discussion

The present study is the first to our knowledge to determine serum MGP concentration in CSU patients as compared with healthy subjects. It has been reported that circulating MGP levels are higher with increasing age and in subjects with advanced atherosclerosis, reflecting the degree of progression of ongoing calcification processes in the arterial wall [11].

We did not observe differences between the healthy subjects and CSU patients in serum concentration of MGP, a biomarker of arterial calcification, which is a clinically significant component of atherosclerosis. On the other hand,

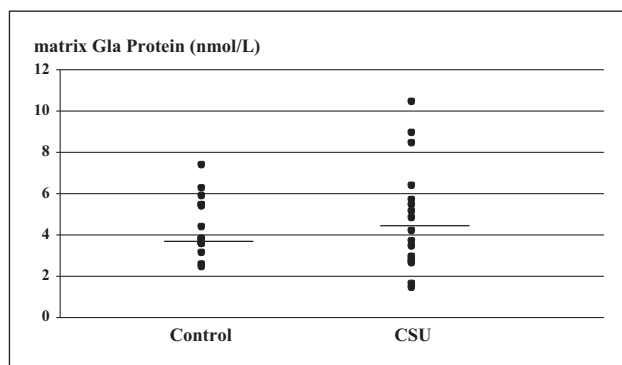


Figure 1. Individual serum concentrations of matrix Gla Protein in CSU patients in comparison to the group of healthy subjects. Horizontal lines represent median value.

serum concentration of IL-6, a biomarker of APR, was significantly higher in CSU patients, which is in accordance with our previous observation showing an association between CSU activity/severity and APR biomarker (IL-6, CRP) concentrations [1, 3]. Interestingly, several mediators of inflammation, such as CRP and cytokines, have been suggested that are able to directly stimulate vascular calcification in some chronic diseases [12]. In our study no correlation was found between MGP and IL-6, indicating that the marker of CSU severity/activity is not significantly associated with circulating MGP. Interestingly, it has been suggested that both circulating APR markers and vascular calcification processes are associated with an increased risk of cardiovascular morbidity and mortality. It seems that APR markers and the calcification process reflect different aspects of the development of atherosclerosis and subsequent cardiovascular events. Limited data show that MGP, when used together with APR markers, may improve the sensitivity for detecting cardiovascular risk factors. These results confirm that CSU is accompanied by a low grade systemic inflammatory state. However, long lasting urticarial inflammation was not paralleled by an increased circulating level of the calcification marker matrix Gla protein. Taking into account that CSU is associated with APR and the metabolic syndrome, the relationship between CSU and atherosclerotic artery calcification deserves further study in larger populations, using imaging techniques such as electron-beam computed tomography. ■

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