

Correspondence

Increased plasma-soluble CD40 concentration in patients with chronic urticaria with positive autologous serum skin test

DOI: 10.1111/bjd.12141

MADAM, Chronic urticaria (CU) can be identified as a mast cell- and basophil-dependent inflammatory disorder of the skin, which is accompanied by an acute-phase response. From the pathogenetic standpoint, the disease can in many cases represent an autoimmune phenomenon.^{1–5}

CD40/CD40L interaction is a critical component of both humoral- and cell-mediated immune response. On the other hand, abnormal signal transduction in the system is involved in the immune-mediated diseases. Soluble CD40 (sCD40), a marker of immunological activation detected in the blood, is thought to regulate CD40/CD40L and signals a negative feedback response.^{6–9}

It has been reported that CD40/CD40L interaction is involved in CU pathogenesis;¹⁰ however, any possible significance of sCD40 in the disease is unknown.

Therefore we have investigated whether sCD40 plasma concentration in CU (i) differs from that in healthy subjects, or (ii) may differ between the autologous serum skin test (ASST)-positive and ASST-negative subtypes of CU.

Sixty-seven patients with active CU were enrolled in the study as described previously.¹¹ The patients were divided into three groups: 22 patients with mild CU, 25 patients with moderate CU and 20 patients with severe urticaria symptoms, using weekly urticaria activity score (UAS),¹¹ as well as into two groups according to ASST response, following the method by Sabroe et al.¹²:

Group I (ASST negative-CU group): 38 patients (23 females and 15 males; median age 38, range 20–45 years);

Group II (ASST positive-CU group): 29 patients (16 females and 13 males; median age 36, range 20–42 years).

The control group consisted of 38 sex- and age-matched healthy subjects. The study was approved by the University Ethics Committee (KNW-6501-46/08).

Quantification of sCD40 was performed in plasma with an enzyme-linked immunosorbent assay (ELISA) kit (IBL, Hamburg, Germany) according to the manufacturer's instructions. Kruskal–Wallis, Mann–Whitney U and Spearman's rank tests were used in the statistical analysis.

Plasma sCD40 concentrations were significantly higher in patients with ASST-positive CU compared with patients with ASST-negative CU and healthy controls [median (quartile

range): 129.2 (121.6–159.2), 103.8 (74.2–132.5) and 105.6 (63.2–131.5) pg mL^{–1}, respectively] (Fig. 1). Plasma sCD40 concentration did not correlate significantly with UAS ($r = -0.14$, $P = 0.47$). In addition, there were no significant differences in plasma sCD40 concentration between the patients with ASST-positive CU with mild, moderate and severe symptoms (Fig. 2).

Our data demonstrate that elevated concentration of circulating sCD40 is present in patients with CU with positive response to ASST, but not in patients with a negative response to ASST, which confirms that different pathomechanisms operate in the two subtypes of CU.

It has been shown that CD40L expression was markedly upregulated on active T cells from patients with autoimmune CU, which might have contributed to increased B-cell proliferation and autoimmune response.¹⁰ In our study, elevated sCD40 plasma concentration in CU suggests increased expression of CD40, resulting in enhanced sCD40 release.

In addition, it is known that through the release of sCD40, B cells may suppress the expression of CD40L on activated T cells⁸ as well as the biological response of B lymphocytes.⁶ The above point to the possible generation of activated, CD40L-positive T cells during an immune response in CU triggering sCD40 release, as a result of increased CD40/CD40L interaction involved in the development of autoimmunity.

It is believed that sCD40 may regulate CD40/CD40L interaction in the negative feedback response,^{6,8} pointing to the theoretical possibility of this molecule being involved in rescue mechanisms to normalize hyperactivity of the CD40/CD40L system in CU.

On the other hand, we hypothesize that abnormal uncontrolled CD40/CD40L interaction occurs in CU, which might

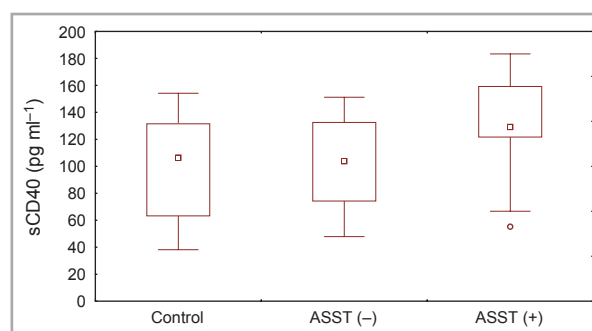


Fig 1. Plasma sCD40 concentration in the control group, ASST-negative CU group and ASST-positive CU group. Control vs. ASST (+) $P = 0.01$; ASST (-) vs. ASST (+) $P = 0.02$.

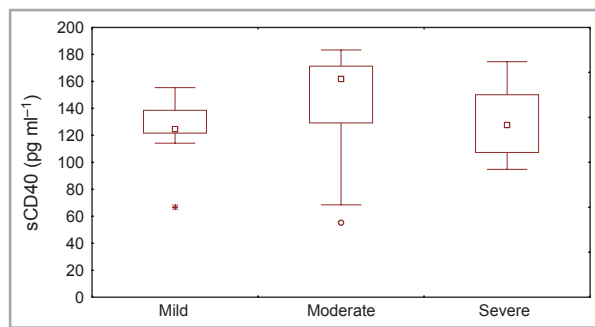


Fig 2. Plasma sCD40 concentration in patients with ASST positive-CU with different disease activity. CU-mild vs. CU-moderate vs. CU-severe, $P = 0.37$ and $P = 0.06$, respectively.

result from a failure of the inhibitory effect of sCD40 to prevent the expression of CD40L on activated T cells in CU. However, the possibility cannot be discarded that sCD40 may not be relevant functionally, but is only a marker of the enhanced CD40/CD40L interaction.

However, increased expression of CD40L on activated T cells has been reported in the blood of patients with CU.¹⁰ We speculate that activation of circulating B cells is the main source of increased plasma sCD40 concentration in ASST-positive CU as a result of enhanced interaction of CD40 with its ligand, CD40L, on activated T cells. These cells have been shown to express high levels of CD40 and to shed biologically active sCD40 *in vitro*, and are considered to be a main source of circulating sCD40.^{6,8}

It should also be mentioned that, in addition to the membrane-bound form, CD40L can also be released as a soluble molecule (sCD40L), which may exert different biological functions. However, data regarding the behaviour of circulating sCD40L in CU are contradictory.¹¹ Similarly to other autoimmune disorders, it is speculated that assessment of sCD40 in plasma might be an index to the detection of the immune origin of the disease. Our observations, along with the earlier results,¹⁰ may indicate that CD40/CD40L interaction plays a role in immune activation in CU.

Clinical Department of Internal Diseases, T. JASINSKA
Allergy and Clinical Immunology, A. KASPERSKA-ZAJAC
Medical University of Silesia, ul. Ceglana 35,
Katowice, Poland
Correspondence: Alicja Kasperska-Zajac.
E-mail: kasperska@plusnet.pl

References

- 1 Kasperska-Zajac A, Sztylc J, Machura E, Jop G. Plasma IL-6 concentration correlates with clinical disease activity and serum C-reactive protein concentration in chronic urticaria patients. *Clin Exp Allergy* 2011; **41**:1386–91.
- 2 Kasperska-Zajac A. Acute-phase response in chronic urticaria. *J Eur Acad Dermatol Venereol* 2012; **26**:665–72.
- 3 Kasperska-Zajac A, Grzanka A, Czecior E et al. Acute phase inflammatory markers in patients with non-steroidal anti-inflammatory drugs (NSAIDs)-induced acute urticaria/angioedema and after aspirin challenge. *J Eur Acad Dermatol Venereol* 2012; (in press).
- 4 Kasperska-Zajac A, Brzoza Z, Rogala B. Sex hormones and urticaria. *J Dermatol Sci* 2008; **52**:79–86.
- 5 Maurer M, Bindslev-Jensen C, Gimenez-Arnau A et al. Chronic idiopathic urticaria (CIU) is no longer idiopathic: time for an update! *Br J Dermatol* 2012; **168**:455–6.
- 6 Fanslow WC, Anderson DM, Grabstein KH et al. Soluble forms of CD40 inhibit biologic responses of human B cells. *J Immunol* 1992; **149**:655–60.
- 7 Schwabe RF, Engelmann H, Hess S, Fricke H. Soluble CD40 in the serum of healthy donors, patients with chronic renal failure, haemodialysis and chronic ambulatory peritoneal dialysis (CAPD) patients. *Clin Exp Immunol* 1999; **117**:153–8.
- 8 van Kooten C, Gaillard C, Galizzi JP et al. B cells regulate expression of CD40 ligand on activated T cells by lowering the mRNA level and through the release of soluble CD40. *Eur J Immunol* 1994; **24**:787–92.
- 9 Björck P, Braesch-Andersen S, Paulie S. Antibodies to distinct epitopes on the CD40 molecule co-operate in stimulation and can be used for the detection of soluble CD40. *Immunology* 1994; **83**:430–7.
- 10 Toubi E, Adir-Shani A, Kessel A et al. Immune aberrations in B and T lymphocytes derived from chronic urticaria patients. *J Clin Immunol* 2000; **20**:371–8.
- 11 Jasinska T, Kasperska-Zajac A. Soluble CD40 ligand is not elevated in plasma of patients suffering from chronic spontaneous urticaria. *Br J Dermatol* 2012; **167**:450–2.
- 12 Sabroe RA, Grattan CEH, Francis DM et al. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; **140**:446–53.

Funding sources: no external funding.

Conflicts of interest: none declared.