

# Plasma soluble CD40 concentration in patients with delayed pressure urticaria

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## Abstract

Very little is known about the immune-inflammatory cascade in delayed pressure urticaria (DPU). It has been suggested that increased activation/expression of CD40 may result in enhanced release of soluble CD40 (sCD40) in chronic urticaria. To investigate release of sCD40 in the course of DPU, plasma sCD40 concentration was measured using ELISA method in 18 adult patients with DPU and 27 age- and sex-matched healthy controls. Plasma sCD40 concentration did not differ significantly in the DPU group as compared to healthy subjects. The present study as well as the earlier contributions, suggest that distinct CD40-signalling activity manifested by sCD40 release may be identified in different types of urticaria. Delayed pressure urticaria is not associated with increased circulating sCD40 concentration, contrary to chronic spontaneous urticaria with positive response to autologous serum skin test.

## Keywords

delayed pressure urticaria, immune activation, inflammation, soluble CD40

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Chronic urticaria (CU) is associated with mast cells activation leading to systemic inflammatory response.<sup>1–3</sup> Delayed pressure urticaria (DPU) is a distinct form of chronic urticaria in several ways: (1) symptoms are elicited by pressure stimuli; (2) prolonged duration of cutaneous/subcutaneous swelling and inflammatory perivascular infiltration of mixed cells in the dermis, mostly mononuclear cells; (3) skin lesions morphologically similar to classic late phase-reaction of IgE-immunity; (4) in many cases systemic symptoms and signs of acute phase response occurs.<sup>4–7</sup> Interestingly, it has been indicated that the local increase in eosinophils and helper T lymphocytes suggests that pressure wheals result from a cellular immune response to so far unknown antigens that are generated at pressure sites.<sup>8</sup> Very little is known about the immune-inflammatory cascade in the initiation and maintenance of DPU lesions. The CD40-CD40L signaling pathway plays an important role in immune response and development of inflammation,<sup>9</sup> including T-cell-mediated inflammatory reactions.<sup>10</sup> Enhanced CD40L-CD40 interaction seems to be involved in

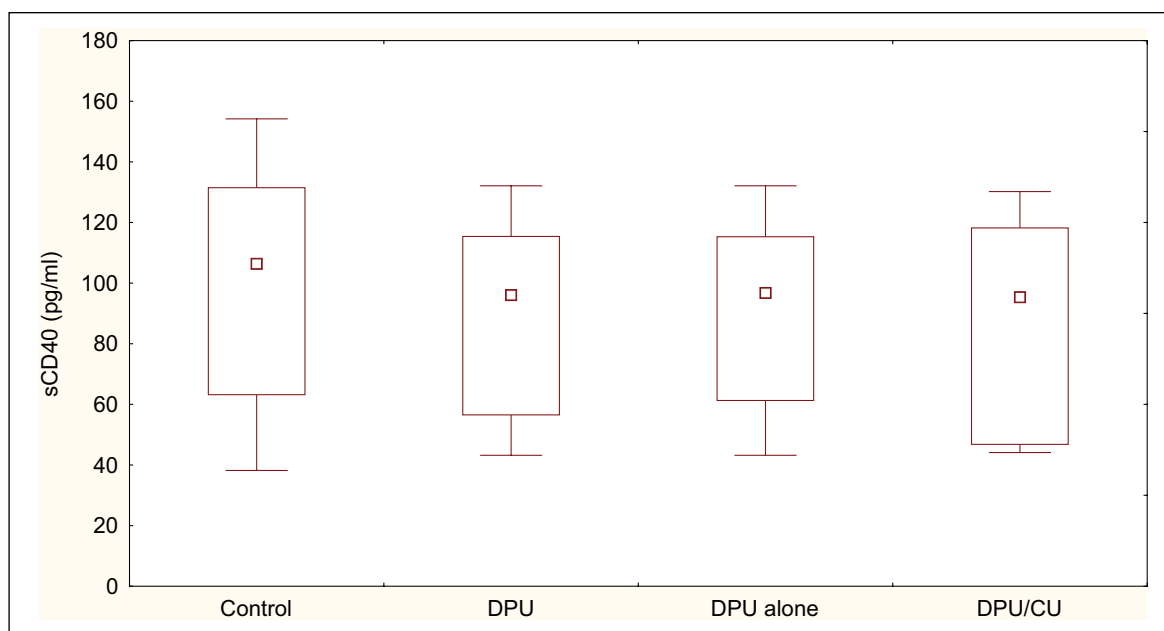
immune and inflammatory diseases.<sup>11</sup> The soluble form of the CD40 molecule (sCD40) is biologically active and may exert suppressive effects on the CD40-CD40L interaction. Therefore, measurement of sCD40 may be useful to assess the CD40 expression and/or immune activation in the CD40-CD40L system.<sup>12,13</sup> Taking into account the above data, the question could be raised whether hyperactivity in the CD40-dependent signalling pathway manifested by increased circulating concentration of sCD40 occurs in DPU patients. Therefore, plasma sCD40 concentration was measured in patients with DPU of varying severity. Eighteen symptomatic patients (11 men, 7 women) with an age range of 26–44

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**Figure 1.** Plasma sCD40 concentration in the control group, DPU as a whole, DPU without concomitant CSU (DPU alone) and DPU with concomitant CSU (DPU/CSU). There were no significant differences between the four groups,  $P < 0.05$ .

years (median age, 37 years): nine patients with pure DPU (DPU alone subgroup) and nine patients with concomitant spontaneous chronic urticaria (DPU/CSU subgroup) were enrolled into the study. All identified causes of urticaria and other diseases had been excluded by appropriate investigation, including routine dental and ENT consultations. All the patients manifested negative response to autologous serum skin test (ASST).<sup>14</sup> Daily spontaneous urticarial activity was measured by assessment of wheals and pruritus on a scale of 0–3 (sum of score, 0–6). Patients scoring 4 or more were included into the study. Seven patients suffered from severe DPU, urticarial lesions still elicited even under slight pressure. In the remaining 11 patients, less extensive urticarial lesions were observed during physical examination. At least 3 weeks before the examination, the patients with severe lesions ceased to take corticosteroids (except for 1 patient). The antihistamines were withdrawn 3–4 days before the study. The control group consisted of 27 non-smoking healthy patients (12 women and 15 men; median age, 36 years; age range, 27–43 years) without any medication. The Local Ethics Commission approved this study and written informed consent was obtained from all participating subjects.

Blood samples anticoagulated with EDTA were obtained between 07:00 and 09:00 by antecubital puncture. Quantification of sCD40 was performed

in plasma with a commercial enzyme-linked immunosorbent assay (ELISA) kit (IBL, Hamburg, Germany) according to the manufacturer's instructions. The intra-assay and inter-assay CV were 5.5% and 7.0%, respectively. Sensitivity of the assay was 7.92 pg/mL.

Results are expressed as median and interquartile ranges. Because data were not distributed normally, non-parametric tests were used. Kruskal-Wallis variance analysis was used for screening differences between the groups. Mann-Whitney  $U$  test was used to compare data between the patient groups and the healthy controls. A probability value of  $P < 0.05$  was assumed to be significant.

Plasma sCD40 concentrations did not differ significantly between DPU patients as a whole and the healthy subjects (96.1 [115.4–58.9] and 105.6 [63.2–128.9] pg/mL). In addition, there were no significant differences between the DPU pure subgroup and the DPU/CSU subgroup and the healthy subjects: 96.8 (61.3–115.3), 95.4 (46.8–118.2) and 105.6 (63.2–128.9) pg/mL, respectively (Figure 1).

It has been demonstrated that CD40L expression was markedly upregulated on active T cells from CU patients, suggesting that CD40–CD40L interaction is involved in CU pathogenesis.<sup>15</sup> However, data regarding behaviour of circulating concentration of sCD40L are conflicting.<sup>16</sup> From the other hand, a role of CD40 molecules in CU has been

poorly investigated. So far, elevated plasma sCD40 concentration was found to be associated with chronic spontaneous urticaria (CSU) with positive response to ASST, but not with negative response to this test.<sup>17</sup> We suggested that an increased sCD40 circulating concentration in CSUASST(+) may be related to stronger immune system activation associated with autoimmune phenomena as well as CD40-signalling might play a role in the pathogenesis of the urticarial.<sup>17</sup> In the present study plasma concentration of sCD40 did not differ significantly in DPU patients, neither in pure DPU nor DPU with concomitant CSU as compared with healthy subjects. These results suggests that enhanced expression/activity of CD40-dependent signalling pathway does not occur in this form of urticaria. In addition, plasma sCD40 concentration in DPU was significantly lower in comparison to previously described CSUASST(+) group.<sup>17</sup> This observation may further confirm that autoreactive phenomena are involved in increased release of sCD40 during urticarial inflammation. Significant limitation of this study is small numbers of subjects, due to low incidence of pure DPU.<sup>18</sup> Pure DPU is uncommon as about 94% of DPU patients suffer from concomitant CSU.<sup>19</sup>

The present study as well as the earlier contribution suggest that distinct CD40-signalling activity manifested by sCD40 release may be identified in different types of urticaria. Contrary to chronic urticaria with positive response to ASST, delayed pressure urticaria is not associated with increased circulating sCD40 concentration, similar to that observed in chronic spontaneous urticaria with negative response to ASST.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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