

Severity of acute and chronic urticaria correlates with D-dimer level, but not C-reactive protein or total IgE

Y. S. Baek, J. Jeon, J. H. Kim and C. H. Oh

Department of Dermatology, College of Medicine, Korea University, Seoul, Korea

doi:10.1111/ced.12413

Summary

Background. Although various scoring systems for measuring urticaria severity have been introduced, most rely on subjective criteria. Therefore, additional objective criteria such as laboratory markers would be helpful adjuncts in making this assessment.

Aim. To evaluate the usefulness of three laboratory markers [D-dimer, C-reactive protein (CRP), and total IgE] in assessing disease severity of both acute urticaria (AU) and chronic urticaria (CU).

Methods. We conducted a retrospective analysis of 94 patients with urticaria. Correlations between the aforementioned laboratory markers and the Urticaria Activity Score (UAS) were calculated.

Results. A substantial proportion of patients with urticaria (acute 43.5%; chronic 39.6%) had an increased D-dimer level. Additionally, there was a significant correlation between D-dimer level and UAS (AU $r = 0.60$, $P < 0.001$; CU $r = 0.37$, $P < 0.05$). However, there was no significant correlation between UAS and either CRP or total IgE.

Conclusions. D-dimer level could be used as a marker of disease severity for both AU and CU. However, CRP and total IgE are not as reliable in predicting disease severity.

Introduction

Various scoring systems for urticaria severity exist. The Urticaria Activity Score (UAS) primarily assesses the key symptoms of urticaria, which are wheals and pruritus.¹ A previous study validated this system by showing that UAS was positively correlated with quality of life impairment in patients with chronic urticaria (CU).² However, this scoring system lacks objectivity, as it relies largely on the patient's descriptions of symptoms. Therefore, an additional objective criterion for evaluating disease severity is needed.

A series of studies by Asero *et al.*^{3–7} previously showed that the coagulation cascade is activated in CU. They found that tissue factor (TF) from eosinophils in patients with CU activated the extrinsic coagulation cascade, resulting in conversion of prothrombin to thrombin.⁸ Thrombin has been shown to be capable of inducing oedema by increasing vascular permeability and stimulating mast cell degranulation, and the authors concluded that thrombin probably plays an important role in the pathogenesis of CU.⁵ Several studies have shown an association between urticaria severity and laboratory markers of the coagulation/fibrinolysis pathway, including prothrombin fragment 1 + 2 (F₁₊₂),^{3,6,7,9} fibrin degradation products (FDP)¹⁰ and D-dimer level.^{6,7,9,10} In addition, C-reactive protein (CRP),^{10–12} total IgE,¹³ interleukin (IL)-6,¹² IL-18,¹⁴ IL-31,¹⁵ vascular endothelial growth factor (VEGF),¹⁶ neopterin¹⁷ and matrix metalloproteinase (MMP)-9¹⁸ have been suggested as possible markers of severity in CU. However, there have been some

Correspondence: Dr Chil Hwan Oh, Department of Dermatology, College of Medicine, Korea University, 97 Gurodong-gil, Guro-gu, Seoul 152-703, Korea
E-mail: choh@korea.ac.kr

Conflict of interest: the authors declare that they have no conflicts of interest.

Accepted for publication 14 December 2013

contradictory reports about the reliability of these potential markers. For example, in a recent study, IL-6, IL-9, IL-18, IL-31, neopterin and VEGF were not increased in CU.¹⁹

Most previous studies have focused primarily on assessing disease severity in patients with CU, whereas studies involving both AU and CU have rarely been reported in the literature. The aim of the present study was to evaluate the ability of some of the aforementioned laboratory markers (D-dimer, CRP and total IgE) to predict disease severity in cases of AU and CU.

Methods

The study was reviewed and approved by the institutional review board of the Korea University Guro Hospital. Patients were informed about the aims and details of the investigation, and gave written informed consent.

Patients

The study was conducted at the Korea University Guro Hospital, which is an 877-bed referral hospital in Seoul, Korea. A retrospective analysis of medical records, laboratory test results and interview responses from patients with urticaria who visited the Department of Dermatology between June 2011 and March 2013 was carried out. Only patients with spontaneous urticaria were included; patients with physical urticarias were excluded based on their clinical history. Patients who were taking medications that could have influenced the coagulation/fibrinolysis pathway such as acetylsalicylic acid, clopidogrel, warfarin or heparin were excluded from the study. Patients who had a medical history of concurrent inflammatory infection, asthma, allergic rhinitis or atopic dermatitis were also excluded because these can affect laboratory results.

Our department has standardized clinical investigations and treatment regimens for patients with urticaria, which includes clinical interview, laboratory tests and standardized antihistamine prescription.

Laboratory tests

At the initial visit, blood samples were collected from all patients. D-dimer levels were measured using an automated latex agglutination method (STA-R Evolution[®]; Diagnostica Stago, Asnières, France), and levels

of < 0.5 µg/L were considered to be within the normal range.

CRP levels were measured by an automated latex-enhanced turbidimetric immunoassay (TBA-200FR[®]; Toshiba Medical System, Tokyo, Japan), and levels of < 5 mg/L were considered to be within the normal range.

Total IgE levels were measured by immunoradiometric assay (SR300[®]I Stratec Biomedical AG, Birkenfeld, Germany), and levels of < 91 IU/mL were considered to be within the normal range for adults. For children, cut-off values for each age group were determined according to the manufacturer's instructions.

Clinical interview

At the follow-up visit, patients were interviewed by trained dermatologists. At that time, a detailed medical history including current medications was obtained. The duration and type of urticaria were also recorded. The average UAS during the time between the initial visit and the follow-up visit (typically, 7–10 days) was measured. Responses to prescribed antihistamines were recorded by the patient as none, poor to partial, or good to complete.

Statistical analysis

Statistical analyses were carried out using SPSS software (version 20.0 for Windows; SPSS Inc, Chicago, IL, USA). Correlations were calculated using Spearman's rank correlation coefficient. Comparisons between the group with raised D-dimer levels and the group with normal D-dimer levels were made using Mann–Whitney *U*-test or χ^2 tests. *P* < 0.05 was considered significant.

Results

Demographic characteristics of patients

The medical records and laboratory results of 116 patients were initially analyzed in this study, and of these, 17 patients with physical urticaria (2 of whom also had atopic dermatitis) were excluded, as were 5 other patients because of the medications they were taking. This left 94 patients, who were included in the study. The patients had a mean age of 39.0 years and a female predominance. Only 13 patients with spontaneous urticaria reported also having angio-oedema (Table 1).

Table 1 Demographic characteristics of patients.

	Type of urticaria		
	Acute (<i>n</i> = 46)	Chronic (<i>n</i> = 48)	Total (<i>n</i> = 94)
Age, years*	38.3 ± 17.3	39.8 ± 17.6	39.0 ± 17.4
Sex, <i>n</i> (%)			
Male	14 (30.4)	23 (47.9)	37 (39.4)
Female	32 (69.6)	25 (52.1)	57 (60.6)
Spontaneous urticaria, <i>n</i> (%)			
Without angio-oedema	40 (87.0)	41 (85.4)	81 (86.2)
With angio-oedema	6 (13.0)	7 (14.6)	13 (13.8)

*Mean ± SD.

Correlation between disease severity and D-dimer level

Mean D-dimer level was 1.3 and 0.79 µg/L (range 0.22–3.89 and 0.06–5.00 µg/L) in patients with AU and CU, respectively, and 20 and 19 patients (43.5% and 39.6%), respectively, were found to have raised levels of D-dimer. D-dimer level significantly correlated with UAS (AU $r = 0.30$, $P < 0.001$; CU $r = 0.37$, $P < 0.05$) (Fig. 1).

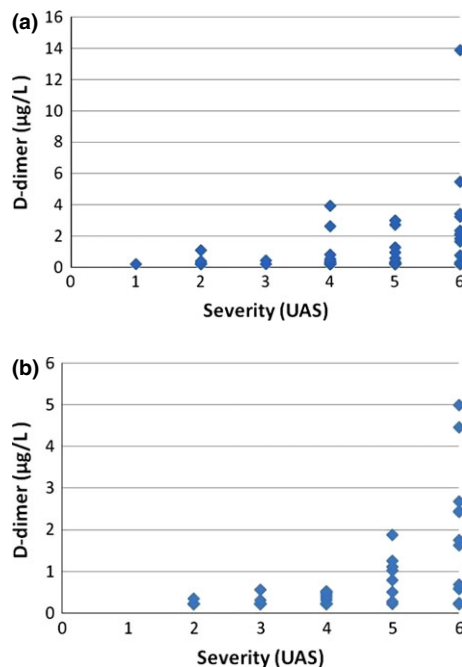
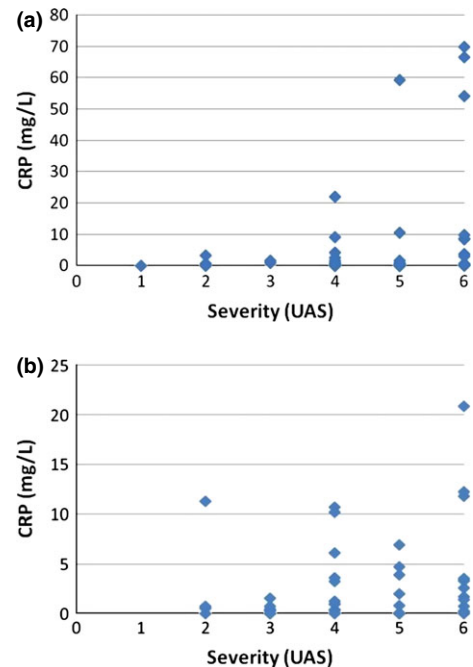
Correlation between disease severity and C-reactive protein

Mean CRP level was 7.61 and 4.56 mg/L (range 0–69.94 mg/L and 0–20.87 mg/L) in patients with

AU and CU, respectively, and 10 and 8 patients (21.7% and 16.7%), respectively, were found to have raised levels of CRP. There was no significant correlation between disease severity and CRP level (AU $r = 0.24$, $P > 0.05$; chronic $r = 0.22$, $P > 0.05$) (Fig. 2).

Correlation between disease severity and total IgE

Mean total IgE was 158.0 and 196.0 IU/mL (range 15.5–51 and 15–1395 IU/mL) in patients with AU and CU, respectively, and 27 and 25 (58.7% and 52.1%), respectively, were found to have raised levels

**Figure 1** Correlation between disease severity and D-dimer level in patients with (a) acute and (b) chronic urticaria. There was a significant correlation between D-dimer level and disease severity patients with acute ($r = 0.60$, $P < 0.001$) and those with chronic ($r = 0.37$, $P < 0.05$) urticaria.**Figure 2** Correlation between disease severity and C-reactive protein (CRP) level in patients with (a) acute and (b) chronic urticaria. There was no significant correlation between CRP level and disease severity in patients with acute ($r = 0.24$, $P > 0.05$) or chronic ($r = 0.22$, $P > 0.05$) urticaria.

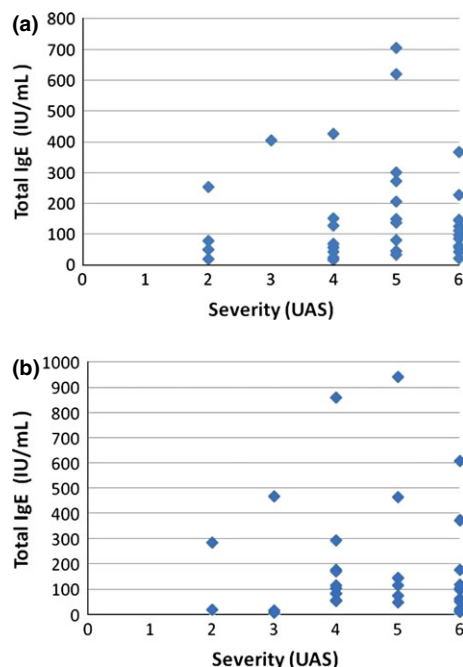


Figure 3 Correlation between disease severity and total IgE in patients with (a) acute and (b) chronic urticaria. There was no significant correlation between total IgE and disease severity in patients with acute ($r = -0.15$, $P > 0.05$) or chronic ($r < 0.01$, $P > 0.05$) urticaria.

of total IgE. There was no significant correlation between disease severity and total IgE (AU $r = -0.15$, $P > 0.05$; chronic $r < 0.01$, $P > 0.05$) (Fig. 3).

Comparisons between the raised D-dimer group and the normal D-dimer group

There were 39 patients (41.8%) with a raised D-dimer level, and 55 (58.5%) with a D-dimer level within normal limits. The raised D-dimer group had significantly higher UAS than the normal D-dimer group. Additional analysis showed no significant difference between the two groups in the response to antihistamine (Table 2).

Discussion

The EAACI/GA²LEN/EDF/WAO guideline recommends the UAS for evaluation of disease activity in patients with urticaria.¹ Although this scoring system is easy and convenient, it depends primarily on subjective descriptions given by patients. Therefore, it lacks a quantitative component, and may not be entirely accurate.¹⁰ Several studies have been conducted to identify additional objective biomarkers of disease

Table 2 Comparisons between the raised and the normal D-dimer groups.

	D-dimer level		<i>P</i>
	Raised (<i>n</i> = 39)	Normal (<i>n</i> = 55)	
Age, years*	42.8 ± 18.2	36.4 ± 16.5	–
Sex, <i>n</i> (%)			
Male	13 (33.3)	24 (43.6)	–
Female	26 (66.7)	31 (56.4)	–
Disease severity (UAS)†	5.2 ± 1.0	3.9 ± 1.3	< 0.001
Response to antihistamine, <i>n</i> (%)			
None	1 (2.6)	5 (9.1)	> 0.05
Poor	13 (33.3)	17 (31.0)	
Good	25 (64.1)	33 (60.0)	

*Mean ± SD; †median ± SD.

severity in cases of urticaria. However, most of these studies, with the exception of one study by Kasperska-Zajac and Brzoza,²⁰ included only patients with CU.

The most widely studied biomarkers for measuring urticaria severity belong to the coagulation/fibrinolysis pathway. Use of these biomarkers was originally suggested by Asero *et al.*³ who reported as indirect evidence that the proportion of skin test-positive patients substantially increases if an autologous plasma skin test (APST) is performed instead of an autologous serum skin test (ASST). They also showed that F_{1+2} levels,¹⁷ which reflect thrombin generation, are significantly raised in patients with CU compared with healthy control subjects. Furthermore, some patients with urticaria experience symptom relief with anticoagulants such as heparin^{4,9} or warfarin,²¹ or with antifibrinolytics such as tranexamic acid.⁴ These results directly support the involvement of the coagulation/fibrinolysis cascade in the pathogenesis of urticaria. Several studies have proposed additional components of this pathway, such as D-dimer level,^{6,7,9,10,17} F_{1+2} ,^{6,9} FDP^{10,17} and soluble fibrin monomer complex⁹ as potential markers for urticaria severity.

As previously described, TF from eosinophils in patients with CU activates the extrinsic coagulation cascade, resulting in conversion of prothrombin to thrombin.⁸ When this conversion takes place, F_{1+2} is released into the circulation. Thrombin subsequently converts fibrinogens to fibrin monomers, which are covalently linked as fibrin polymers by factor XIIIa. Finally, fibrin is degraded by plasmin, which creates FDP and exposes the D-dimer antigen.^{10,22} Therefore, the D-dimer level reflects formation (coagulation pathway) and digestion (fibrinolysis) of fibrin.¹⁰ The present study showed that a substantial percentage of

patients with urticaria had raised D-dimer levels, and that these correlated significantly with disease severity. As expected, patients with raised D-dimer levels had a higher UAS than patients with normal D-dimer levels. These results suggest that D-dimer level can be used as a reliable marker of disease severity for both AU and CU. Additionally, these results suggest that the coagulation/fibrinolysis pathway might be activated in a subset of patients with urticaria. However, whether the elevation of D-dimer level contributes to the pathogenesis of urticaria or is an epiphenomenon remains to be determined. It is important to note that low D-dimer level can also be found in patients with high UAS. This suggests that activation of the coagulation/fibrinolysis pathway is not always present in the pathogenesis of urticaria, and raises the possibility of different pathogenesis among patients.

Interestingly, response to antihistamine did not differ significantly between the raised and normal D-dimer groups. Therefore, urticaria with a raised D-dimer level does not necessarily require treatment with an anticoagulant or antifibrinolytics, as most cases will respond to a traditional antihistamine. However, this finding was not consistent with the findings of a recent study that suggested D-dimer as a biomarker for antihistamine-resistant CU.²³ Further studies are required to clarify the relationship between D-dimer and antihistamine response.

It is important to recognize that a raised D-dimer level in patients with urticaria is not due to an ongoing intravascular coagulopathy such as active thromboembolism. Fujii *et al.*²⁴ previously reported that activation of the coagulation/fibrinolysis cascade occurs extravascularly, primarily in the dermis. They also found that thrombin generated in patients with urticaria is instantly inactivated by tissue antithrombin III, and that fibrinogen degradation products flow backwards into the systemic circulation through the hyperpermeable vasculature.

CRP is known to be a very sensitive marker for AU-phase responses associated with conditions such as infection, inflammatory disease, malignancy and trauma.²⁵ Previous studies have shown that CRP levels are raised in certain patients with CU, and that CRP levels correlate with disease activity.^{10–12} Additionally, previous studies reported that CRP levels correlated significantly with levels of IL-6.¹² Some investigators have suggested that IL-6 elevation is characteristic of the active phase of CU, and that increased CRP levels are caused by IL-6.^{10,25} The present study failed to show a significant correlation between CRP level and urticaria severity. Therefore,

CRP cannot as yet be considered a definite marker for urticaria severity, and further studies are needed to determine the true relationship between urticaria severity and CRP level.

Kessel *et al.*¹³ previously showed a significant association between increased total IgE and CU severity. They hypothesized that this relationship may be explained by the effects of IgE on mast cell activation and degranulation. In our study, a substantial percentage of patients had increased levels of total IgE. However, there was no significant relationship between total IgE level and urticaria severity. This may be due to differences in urticaria severity scoring methods or statistical analysis.

The study had several limitations. Firstly, it was a retrospective study with a limited number of patients at a single referral hospital. In addition, it did not assess laboratory markers repeatedly, and did not include other laboratory markers such as F₁₊₂ and FDP. Further prospective studies in larger populations conducted at multiple centre are required to expand further on our findings.

Conclusion

D-dimer level can be used as a marker of disease severity for both acute and chronic urticaria. However, CRP and total IgE are not as reliable in predicting disease severity.

What's already known about this topic?

- Several laboratory markers, including D-dimer, CRP and total IgE, have been used as possible markers of severity in CU.

What does this study add?

- D-dimer level can be used as a marker of disease severity for both AU and CU.
- CRP and total IgE are not reliable markers in predicting disease severity for either AU or CU.

Acknowledgements

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of

Education, Science and Technology (grant no. 2012R1A1A2006556).

References

- Zuberbier T, Asero R, Bindslev-Jensen C *et al*. EAACI/GA (2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009; **64**: 1417–26.
- Mlynek A, Zalewska-Janowska A, Martus P *et al*. How to assess disease activity in patients with chronic urticaria? *Allergy* 2008; **63**: 777–80.
- Asero R, Tedeschi A, Riboldi P, Cugno M. Plasma of patients with chronic urticaria shows signs of thrombin generation, and its intradermal injection causes wheal-and-flare reactions much more frequently than autologous serum. *J Allergy Clin Immunol* 2006; **117**: 1113–17.
- Asero R, Tedeschi A, Cugno M. Heparin and tranexamic Acid therapy may be effective in treatment-resistant chronic urticaria with elevated D-dimer: a pilot study. *Int Arch Allergy Immunol* 2010; **152**: 384–9.
- Asero R, Tedeschi A, Coppola R *et al*. Activation of the tissue factor pathway of blood coagulation in patients with chronic urticaria. *J Allergy Clin Immunol* 2007; **119**: 705–10.
- Asero R, Tedeschi A, Riboldi P *et al*. Severe chronic urticaria is associated with elevated plasma levels of D-dimer. *Allergy* 2008; **63**: 176–80.
- Asero R, Cugno M, Tedeschi A. Activation of blood coagulation in plasma from chronic urticaria patients with negative autologous plasma skin test. *J Eur Acad Dermatol Venereol* 2011; **25**: 201–5.
- Cugno M, Marzano AV, Asero R, Tedeschi A. Activation of blood coagulation in chronic urticaria: pathophysiological and clinical implications. *Intern Emerg Med* 2010; **5**: 97–101.
- Takeda T, Sakurai Y, Takahagi S *et al*. Increase of coagulation potential in chronic spontaneous urticaria. *Allergy* 2011; **66**: 428–33.
- Takahagi S, Mihara S, Iwamoto K *et al*. Coagulation/fibrinolysis and inflammation markers are associated with disease activity in patients with chronic urticaria. *Allergy* 2010; **65**: 649–56.
- Tedeschi A, Asero R, Lorini M *et al*. Plasma levels of matrix metalloproteinase-9 in chronic urticaria patients correlate with disease severity and C-reactive protein but not with circulating histamine-releasing factors. *Clin Exp Allergy* 2010; **40**: 875–81.
- Kasperska-Zajac A, Sztylec 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.
- Kessel A, Helou W, Bamberger E *et al*. Elevated serum total IgE—a potential marker for severe chronic urticaria. *Int Arch Allergy Immunol* 2010; **153**: 288–93.
- Tedeschi A, Lorini M, Suli C, Asero R. Serum interleukin-18 in patients with chronic ordinary urticaria: association with disease activity. *Clin Exp Dermatol* 2007; **32**: 568–70.
- Raap U, Wiczorek D, Gehring M *et al*. Increased levels of serum IL-31 in chronic spontaneous urticaria. *Exp Dermatol* 2010; **19**: 464–6.
- Tedeschi A, Asero R, Marzano AV *et al*. Plasma levels and skin-eosinophil-expression of vascular endothelial growth factor in patients with chronic urticaria. *Allergy* 2009; **64**: 1616–22.
- Ciprandi G, De Amici M, Berardi L *et al*. Serum neopterin levels in spontaneous urticaria and atopic dermatitis. *Clin Exp Dermatol* 2011; **36**: 85–7.
- Kessel A, Bishara R, Amital A *et al*. Increased plasma levels of matrix metalloproteinase-9 are associated with the severity of chronic urticaria. *Clin Exp Allergy* 2005; **35**: 221–5.
- Metz M, Krull C, Maurer M. Histamine, TNF, C5a, IL-6,-9,-18,-31,-33, TSLP, neopterin, and VEGF are not elevated in chronic spontaneous urticaria. *J Dermatol Sci* 2013; **70**: 222–5.
- Kasperska-Zajac A, Brzoza Z. Increased D-dimer concentration in plasma of patients with severe acute urticaria. *Br J Dermatol* 2009; **161**: 1409–10.
- Parslew R, Pryce D, Ashworth J, Friedmann PS. Warfarin treatment of chronic idiopathic urticaria and angio-oedema. *Clin Exp Allergy* 2000; **30**: 1161–5.
- Adam SS, Key NS, Greenberg CS. D-dimer antigen: current concepts and future prospects. *Blood* 2009; **113**: 2878–87.
- Asero R. D-dimer: a biomarker for antihistamine-resistant chronic urticaria. *J Allergy Clin Immunol* 2013; **132**: 983–6.
- Fujii K, Usuki A, Kan-No Y, Ohgou N. Elevation of circulating thrombin-antithrombin III complex and fibrin degradation products in urticaria: a laboratory finding unrelated to intravascular coagulopathy. *J Dermatol* 2008; **35**: 308–10.
- Kasperska-Zajac A. Acute-phase response in chronic urticaria. *J Eur Acad Dermatol Venereol* 2012; **26**: 665–72.