

Misbah Noshela GHAZANFAR¹
Simon Francis THOMSEN^{1,2}

¹ Bispebjerg Hospital,
Department of Dermatology,
Copenhagen,
Denmark

² University of Copenhagen,
Center for Medical Research Methodology,
Department of Biomedical Sciences,
Copenhagen,
Denmark

Reprints: Misbah Noshela Ghazanfar
<misbah.noshela.ghazanfar@regionh.dk>

D-dimer as a potential blood biomarker for disease activity and treatment response in chronic urticaria: a focused review

Chronic urticaria is an itchy skin disease, which is treated with antihistamines; however, a large group of patients are unresponsive to antihistamines alone and are thus treated with omalizumab, although a small fraction of these patients have particularly recalcitrant disease. Currently, there are no reliable biomarkers available to assess disease activity/severity and treatment response in chronic urticaria patients. However, it has been reported that high levels of D-dimer are observed during disease activity and are significantly reduced during periods of remission. We present a focused overview of studies investigating plasma D-dimer level as a biomarker for disease activity and treatment response in patients with chronic urticaria.

Key words: chronic urticaria, D-dimer, biomarker, disease activity, treatment response

Article accepted on 29/03/2018

Chronic urticaria (CU) is an itchy skin disease characterized by wheals and/or angioedema that lasts for at least six weeks. CU can be subdivided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CINDU). CINDU is induced, for example, by physical stimuli such as heat, cold, pressure or sun exposure [1].

The recommended treatment for CU by international guidelines is non-sedating antihistamines once daily as first-line therapy; if no improvement is observed it is recommended to increase the dose of antihistamine up to four-fold. Third-line options include add-on therapy of omalizumab, cyclosporine or montelukast [1]. Up to half of all patients are unresponsive to antihistamines alone.

In up to 45% [2] of the cases, CSU has an autoimmune basis with circulating histamine-releasing auto-antibodies directed against IgE and/or the high affinity IgE receptor FcRI on mast cells and basophiles. Further, some patients have autoreactive antibodies directed against thyroid peroxidase [2] and recent data shows that autoimmunity is one of the most frequent causes of CSU [3].

Several studies have investigated potential biomarkers of CSU; however, currently there are no reliable biomarkers available to assess disease activity/severity or treatment response. Some patients with CSU show an activation of the tissue factor pathway of the coagulation cascade and, in patients with severe disease activity, this activation can increase plasma levels of D-dimer [4]. The elevation of D-dimer has also been reported in patients with angioedema due to C1-inhibitor deficiency. Furthermore, it has been reported that high levels of D-dimer during disease activity are significantly reduced during periods of remission. Nonetheless, the increased levels of D-dimer during disease exacerbation are not associated with an increased risk of thrombosis [5].

Herein, we review studies of plasma D-dimer level as a biomarker for disease activity and treatment response in patients with CU.

Literature search

A systemic literature search was conducted in PubMed and EMBASE using the search terms: “chronic urticaria AND D-dimer”, “urticaria AND D-dimer”, “urticaria AND coagulation” and “CSU AND D-dimer”, “CSU AND biomarkers”, and “urticaria AND biomarkers”. All studies were reviewed by the first author, and retrospective and prospective case series and observational studies published since 2008 and including patients with urticaria related to D-dimer and disease activity were included. Reference lists were scrutinized for completion.

The literature search identified a total of 12 studies; three retrospective, one prospective, and four case-control studies related to plasma D-dimer levels and disease activity, as well as four studies related to plasma D-dimer levels and treatment response (*table 1*).

Main findings

D-dimer and disease activity in chronic urticaria

Several studies have shown that D-dimer is related to disease activity in patients with CU. A retrospective study from Japan [6] examined the relationship between D-dimer, CRP, fibrin degradation products (FDP), and disease activity in 82 patients with CU. The patients were treated with antihistamines with or without concomitant leukotriene antagonists, corticosteroids, and/or immunosuppressive drugs, whereas some of the patients were also treated with tranexamic acid, warfarin, heparin, and protease inhibitors. FDP was elevated in 21% of the patients, while D-dimer was elevated in 35% of the patients, including all of the patients with elevated FDP. Elevated CRP

Table 1. Overview of patient characteristics and assessment outcomes in included studies.

Source	Patient characteristics							Assessment	
Author	Country	Study design	Number of patients	Age range (years)	Gender	Diagnosis	Disease activity	D-dimer	Other
					F	M			
Takahagi <i>et al.</i> (2010) [7]	Japan	Retrospective	82	4-80	60	22	CSU	Decrease when disease severity improved	FDP and CRP were reduced when disease severity improved
Triwongwanarat <i>et al.</i> (2013) [9]	Thailand	Retrospective	120	16-73	90	30	CIU (CSU)	UAS7 score was used	Plasma D-dimer level was measured in 58 patients. Decrease in disease activity led to decrease in D-dimer level
Baek <i>et al.</i> (2014) [8]	Korea	Retrospective	94	39±17.4	57	37	AU and CU	UAS7 score was used	Mean D-dimer level was 1.3 and 0.79 µg/L in patients with AU and CU. 39 patients had increased level of D-dimer
Asero <i>et al.</i> (2010) [13]	Italy	Prospective	68	-	-	-	CU		Higher levels of plasma D-dimer were seen in antihistamine-resistant CU patients
Asero (2013) [20]	Italy	Prospective	91	11-85	69	22	CU	UAS score was used. Mean UAS = 3.6	Elevated D-dimer levels were seen in patients with antihistamine-resistant moderate CU
Asero (2015) [21]	Italy	Prospective	29	11-75	20	9	CU	UAS was used. Mean UAS = 4.3	D-dimer level was elevated in 60% of the patients. 7 of 18 patients with elevated D-dimer experienced a good response to cyclosporine treatment
Asero <i>et al.</i> (2008) [12]	Italy	Case-control	8				CU		Plasma D-dimer was higher in patients with severe CU
Kasperska-Zajac and Brzoza, (2009) [14]	Poland	Case-control	17	21-42	10	7	AU	Disease activity was defined based on numbers of wheals from 1 (slight) to 4 (severe)	D-dimer level was higher in patients with severe disease activity compared to mild or moderate
Asero <i>et al.</i> (2011) [6]	Italy	Case-control	43	17-72	15	28	CU		Significant correlations were seen between disease severity, prothrombin fragments, and plasma D-dimer level
Criado <i>et al.</i> (2013) [13]	Brazil	Case-control	37	24-69	24	13	CU and psoriasis	Disease activity was defined as presence of active cutaneous lesions. 12 patients had active CU. 10 patients were in remission	Mean D-dimer level was 869 ng/mL (normal <500 ng/mL)
Farres <i>et al.</i> (2015) [11]	Egypt	Case-control	30	29,5 ± 8.76	18	12	CSU	Significant decrease in plasma D-dimer level	FVIIa was increased in patients with CSU

AU: acute urticaria; ASST: autologous serum skin testing; APST: autologous plasma skin testing; FVIIa: factor VIIa; CSU: chronic spontaneous urticaria; CIU: chronic inducible urticaria; CU: chronic urticaria; AU: acute urticaria; UAS: Urticaria Activity Score; FDP: fibrin degradation products; CRP: C-reactive protein; ASST: autologous serum skin testing.

was observed in 23% of the patients. A total of 57% of the patients reported "severe" disease activity (more than 50 wheals per day), and these patients also had higher levels of FDP, D-dimer, and CRP than patients with moderate or mild disease activity. A significant reduction in FDP, D-dimer, and CRP was seen when disease activity was reduced ($P < 0.01$ for FDP and $P < 0.05$ for D-dimer and CRP).

Another retrospective Korean study [7] investigated whether various laboratory markers, such as D-dimer, CRP, and total IgE, were associated with disease severity among adult patients with CSU ($n=48$) or acute urticaria (AU) ($n=46$), whereas patients with CINDU and patients who were taking medication that could influence the coagulation pathway were excluded. Angioedema was reported by 13 patients. A slightly higher level of D-dimer was observed among patients with AU ($1.3 \mu\text{g/L}$) compared to patients with CSU ($0.7 \mu\text{g/L}$). Further, D-dimer levels significantly correlated with the Urticaria Activity Score (UAS) ($r=0.30$; $P < 0.001$) and CU ($r=0.37$; $P < 0.05$) and, specifically, patients with elevated D-dimer had significantly higher UAS than patients with normal D-dimer. However, no significant correlation was observed between UAS and CRP or IgE [6].

A large retrospective study from Thailand [8] examined the relationship between plasma D-dimer levels and disease severity in 120 patients (30 male and 90 female) with CU, of whom 58 had abnormal plasma D-dimer levels. The 120 patients were categorized into three groups according to disease activity; mild, moderate, and severe disease activity was observed in 63 (52.5%), 37 (30.8%) and 20 (16.7%) patients, respectively. Six patients also had angioedema, while 36 patients had a history of atopy and 25 patients had a family history of atopy. Abnormal D-dimer levels were seen in 58 (48.3%) of the patients. In 96 of the patients, autologous serum skin testing (ASST) and autologous plasma skin testing (APST) was performed. ASST was positive in 34.4% of the patients while APST was positive in 36.5%. Plasma D-dimer level was also elevated in the APST-negative group, however, no overall significant difference in plasma D-dimer level was observed between the APST-positive and APST-negative groups, nor in the ASST-positive and ASST-negative groups. Of the more severe disease activity group, 16 of the 20 patients had abnormal plasma D-dimer levels. The median plasma D-dimer level in the severe group was $1,410.8 \text{ ng/mL}$ compared to 317.4 ng/mL and 687.3 ng/mL in the mild and moderate disease groups, respectively. A positive correlation between plasma D-dimer levels and severity of disease activity was seen ($P < 0.05$; $r=0.537$). Likewise, a Brazilian case-control study [9] investigated the association between D-dimer serum level and disease activity in CU. Thirty-seven patients were divided into three groups: 12 patients with active CU, 10 patients with CU in remission, and 15 control patients with psoriasis. Increased levels of D-dimer were seen in all 12 patients with active CU, ranging from 589 to $1,400 \text{ ng/mL}$. The patients with CU in remission had normal D-dimer levels, while only one patient with psoriasis had elevated D-dimer. Similarly, based on a case-control study of 30 patients with CSU and 30 healthy subjects from Egypt [10], the relationship between biomarkers of importance in the coagulation cascade and disease severity and activity in CSU was investigated. Plasma levels of D-dimer and factor VIIa were significantly elevated among patients with active CSU com-

pared to healthy controls (662.5 ng/mL versus 150 ng/mL [$P < 0.001$] for D-dimer; 330 versus 100% [$P < 0.001$] for FVII). Further, there was a significant difference in D-dimer levels according to differences in the level of disease severity (1-10 versus 11-50 versus $+50$ wheals); however, FVIIa levels did not differ according to disease severity. Similar observations were reported by Asero *et al.* [11] who observed that plasma D-dimer levels were significantly elevated in eight patients with severe CU compared to 13 patients with mild disease activity. Marked activation of the coagulation cascade and fibrinolysis was seen; however, it was not possible to determine whether this activation was the cause of CU or associated with an intensification of the disease.

In a short prospective study [12] of 68 CU patients, D-dimer levels and antihistamine resistance was investigated. Plasma D-dimer levels were measured and the patients were treated with 10 mg cetirizine for two weeks. For non-responders, the dose was increased to 30 mg cetirizine for one week. Non-responders with increased levels of D-dimer were offered treatment with nadroparin and tranexamic acid. Fourteen of the 68 patients had elevated D-dimer levels and 12 of the 14 patients with elevated D-dimer did not respond to antihistamines. Eight patients were treated with anticoagulant treatment and five patients showed good response to anticoagulant therapy. Furthermore, the study concluded that elevated D-dimer levels in CU patients indicate a more severe disease activity.

In one study [13], 17 patients with AU were divided into two groups according to disease activity. Thirty healthy subjects were included as a control group. D-dimer levels were significantly higher in patients with severe AU compared with patients with mild/moderate AU and healthy subjects (2.6 [range: $2.2-4.5$] versus 0.17 [range: $0.05-0.18$] versus 0.14 [range: $0.08-0.22$], respectively; $P < 0.001$).

In an Italian study of 43 patients with CU [5], APST-positive patients were compared with APST-negative patients and healthy subjects. Seven patients had elevated prothrombin fragments and plasma D-dimer levels. Significant correlations were observed between disease severity, prothrombin fragments ($r=0.685$; $P=0.003$), and plasma D-dimer level ($r=0.704$; $P=0.002$). Further, it was observed that patients with negative APST had higher plasma D-dimer level compared to healthy subjects, but significantly lower plasma D-dimer levels compared to patients with positive APST.

D-dimer and treatment response in chronic urticaria

Asero *et al.* [14] investigated plasma D-dimer levels in patients with severe CU treated with cyclosporine. The study included 29 patients with severe antihistamine-resistant CU. All patients had been treated with different antihistamines and oral prednisolone, but symptoms had relapsed as soon as the treatment was discontinued. Cyclosporine was administered for a minimum of three months and plasma D-dimer levels were measured before and during treatment or at the end of treatment. Baseline D-dimer levels were elevated in 60% of the patients and seven of 18 patients (39%) with elevated plasma D-dimer responded well to the treatment compared to 10 of 11 (91%) patients with normal D-dimer levels. D-dimer levels were

shown to follow the clinical response to cyclosporine in most of the patients [14].

In an Egyptian case-control study [10] comprising 30 patients with active CSU and 30 healthy subjects, a significant decrease in D-dimer and FVIIa ($P < 0.001$) was seen in 25 patients with CSU who were available for follow-up after remission. Likewise, Asero *et al.* [11] reported a decrease in D-dimer in two patients. One patient had severe exacerbation of CSU and was treated with oral corticosteroids, antihistamines, and low-molecular-weight heparin. The plasma levels of D-dimer were reduced from 603 to 160 pmol/L.

A larger prospective study also from Italy [15] included 91 adult patients with CSU. At the first visit, antihistamine therapy was stopped to assess disease severity. UAS was used from day 5 to 7 and all patients were then given 10 mg of cetirizine daily for seven to 14 days. If no response was observed, the dose was increased two-fold for four days and then three-fold for another three days. The response was classified as “excellent”, “good”, “partial”, “poor” or “absent”. Plasma D-dimer levels were measured on day 7 to 14 after the first visit. The response to cetirizine treatment was “excellent” in 45% of the patients, “good” in 15%, “partial” in 5%, and “poor” in 25% of the patients, while 9% of the patients were non-responders. Overall, D-dimer levels were elevated in 33% of the patients and none of the patients who responded “excellent” to the treatment had increased D-dimer levels. D-dimer was elevated in 21% of the patients who showed “good” response, and increased in as many as 60% and 78% of the patients who responded “partial” and “poor”, respectively. All non-responders except one had increased levels of plasma D-dimer.

In a recent report from Italy [16], 32 patients with severe CSU (UAS7 score > 30) and antihistamine refractory patients were included and treated with omalizumab at 300 mg every fourth week for three months. Baseline D-dimer levels were elevated in 19 patients (59%). Twenty-four (75%) patients showed complete response to omalizumab. Furthermore, 15 of 19 patients (79%) of those who had elevated D-dimer levels showed complete response to omalizumab. Among non-responders, D-dimer plasma levels increased after omalizumab administration from 787 ± 206 to $1,230 \pm 467$ ng/mL. It was concluded that D-dimer plasma levels decrease according to the clinical response to treatment. Similar observations were seen in a case report [17], which included a CSU patient with severe disease activity. The patient was unresponsive to antihistamine treatment and showed partial response to prednisolone. A weekly UAS score of 38 was calculated. The patient was treated with omalizumab at 300 mg every fourth week. D-dimer levels corresponded to UAS7, and were considered as a marker for disease activity and treatment response.

Discussion

There is a relatively sparse literature concerning plasma D-dimer as a potential biomarker for disease severity/activity and treatment response in CU. The available studies, however, suggest that D-dimer can be used as a potential biomarker for disease activity in patients with CSU [7-12]. In particular, it has been shown that D-dimer levels signifi-

cantly correlate with UAS scores. However, no significant association has been observed between D-dimer levels and APST or ASST [5]. Furthermore, it has been suggested that D-dimer can be used as a monitoring tool for treatment response in patients with severe disease activity as increased D-dimer levels are often associated with refractory disease and poor response to treatment, notably as a marker for antihistamine-resistant CU [14].

D-dimer is a FDP, which reflects the expression of tissue factor by eosinophils, the activation of the coagulation cascade, and thrombin generation. A recent study [18] showed that the extrinsic pathway of the clotting cascade is activated in CU and disease activity is associated with the coagulation cascade. The plasma levels of D-dimer are usually increased due to eosinophil activation in CU [14] and thrombin generation. Thrombin generation increases vascular permeability and induces degranulation of mast cells [4].

While D-dimer appears to play an important role as a biomarker for CU, there are other biomarkers, which have also shown some potential. One such biomarker is the basophil histamine release (HR) assay, which has been linked to treatment response in CSU patients. In a study by Ghazanfar *et al.* [19], a larger fraction of CSU patients with a negative HR assay experienced complete or almost complete response to omalizumab treatment compared to HR-positive CSU patients. Similar observations were made in another study [20], in which an analysis of omalizumab responders showed that HR-positive CSU patients only responded after a second injection of omalizumab, and the median time to response was 29 days compared to two days for HR-negative patients. Thus, a positive HR test might be useful to predict a less favourable treatment response to omalizumab in CU patients; however, more studies are needed to investigate this further.

Based on several studies from different countries, D-dimer appears to be promising as a biomarker for CU. However, it is not normally used in the everyday clinical setting to predict disease activity/severity or treatment response. One of the reasons for this could be a lack of evidence of whether D-dimer is specifically increased in patients with urticaria, as it can be increased in other diseases as well. Additionally, there is a need for larger and more thorough studies. Most of the current evidence is based on experience from single centres and small retrospective studies. It would be interesting to carry out larger prospective multinational studies and studies in which treatment choice and dose were determined according to plasma D-dimer levels before treatment. Further, more studies are needed to evaluate the role of D-dimer as a potential biomarker in different subtypes of CU, according to various disease characteristics and among patients with comorbidities. ■

Disclosure. *Conflicts of interest: none.*

References

1. Zuberbier T, Aberer W, Asero R, *et al.* The EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014; 69: 868-87.

2. 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.
3. Kolkhir P, Church MK, Weller K, et al. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol* 2017; 139: 1772-81.
4. Kolkhir P, Borzova E, Grattan C, et al. Autoimmune comorbidity in chronic spontaneous urticaria: a systematic review. *Autoimmun Rev* 2017; 16: 1196-208.
5. Kolkhir P, André F, Church MK, et al. Potential blood biomarkers in chronic spontaneous urticaria. *Clin Exp Allergy* 2017;47: 19-36.
6. 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.
7. 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.
8. Baek YS, Jeon J, Kim JH, Oh CH. Severity of acute and chronic urticaria correlates with D-dimer level, but not C-reactive protein or total IgE. *Clin Exp Dermatol* 2014; 39: 795-800.
9. Triwongwanarat D, Kulthanan K, Chularojanamontri L, Pinkaew S. Correlation between plasma D-dimer levels and the severity of patients with chronic urticaria. *Asia Pac Allergy* 2013; 3: 100-5.
10. Criado PR, Antinori LC, Maruta CW, Reis VM. Evaluation of D-dimer serum levels among patients with chronic urticaria, psoriasis and urticarial vasculitis. *An Bras Dermatol* 2013; 88: 355-60.
11. Farres MN, Refaat M, Melek NA, et al. Activation of coagulation in chronic urticaria in relation to disease severity and activity. *Allergol Immunopathol (Madr)* 2015; 43: 162-7 .
12. 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.
13. 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.
14. Kasperska-Zajac A, Brzoza Z. Increased D-dimer concentration in plasma of patients with severe acute urticaria. *Br J Dermatol* 2009; 161: 1409-10.
15. Asero R. Plasma D-dimer levels and clinical response to ciclosporin in severe chronic spontaneous urticaria. *J Allergy Clin Immunol* 2015; 135: 1401-3.
16. Asero R, Marzano AV, Ferrucci S, Cugno M. D-dimer plasma levels parallel the clinical response to omalizumab in patients with severe chronic spontaneous urticaria. *Int Arch Allergy Immunol* 2017; 172: 40-4.
17. Asero R. Serial D-dimer plasma levels in a patient with chronic spontaneous urticaria developing resistance to omalizumab. *Clin Exp Dermatol* 2017; 42: 667-9.
18. Asero R, Tedeschi A, Coppola R. Activation of the tissue factor pathway of blood coagulation in patients with chronic urticaria. *J Allergy Clin Immunol* 2007; 119: 705-10.
19. Ghazanfar MN, Sand C, Thomsen SF. Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: evaluation of 154 patients. *Br J Dermatol* 2016; 175: 404-6.
20. Asero R. D-dimer: a biomarker for antihistamine-resistant chronic urticaria. *J Allergy Clin Immunol* 2013; 132: 983-6.
21. Asero R. Plasma D-dimer levels and clinical response to ciclosporin in severe chronic spontaneous urticaria. *J Allergy Clin Immunol* 2015; 135: 1401-3.