

Evaluation of Plasma D-dimer Levels in Chronic Idiopathic Urticaria (CIU)

N Ragab, S Salem, N Hussein

Citation

N Ragab, S Salem, N Hussein. *Evaluation of Plasma D-dimer Levels in Chronic Idiopathic Urticaria (CIU)*. The Internet Journal of Dermatology. 2009 Volume 8 Number 1.

Abstract

Background: Chronic idiopathic urticaria (CIU) is a common form of chronic urticaria in which no precise causal factors can be identified. The objective of this study is to estimate the plasma levels of D-dimer in patients with chronic idiopathic urticaria, to assess its possible role in CIU and to correlate such levels with the disease severity. **Methods:** Twenty patients with CIU; ten with urticaria of known cause and ten apparently healthy subjects matched for age and sex were included in this study. Plasma D-dimer was estimated for all groups while in the acute attack and after remission of symptoms. **Results:** Plasma D-dimer was significantly elevated in CIU patients, it was also significantly elevated in patients with CU of known cause with no significant difference between the two groups. Higher levels of D-dimer were detected in relation to the severity of urticaria that a highly significant difference was detected between severe and mild cases. D-dimer plasma levels after complete remission of symptoms show a dramatic drop which was significantly higher during the acute exacerbation of the disease. **Conclusions:** Plasma D-dimer could be a useful marker of disease severity and activity in CU patients.

INTRODUCTION

Chronic urticaria (CU) is a common disorder presenting as cutaneous wheals with or without angioedema for more than 6 weeks, occurring on a continuous or recurrent basis over prolonged periods of time and caused by release of vasoactive mediators from mast cells within the dermis [1]. The majority of patients have no definable underlying disease or specific physical precipitants, and can be termed 'chronic idiopathic urticaria' (CIU) [2]. The etiology and pathogenesis of CIU are poorly understood. However, in 30–50% of cases, autoimmune processes have been suggested as causative factors [3, 4]. The pathomechanism remains elusive in those cases of CIU in which autologous serum skin test (ASST) is negative and no histamine-releasing auto- antibodies can be demonstrated.

It has been reported that mast cells may show profibrinolytic activity [5]. The supernatants of cultured mast cells are capable of inducing the conversion of plasminogen to plasmin and of lysing a fibrin clot [6]. Moreover, skin mast cells may affect hemostasis by prolonging bleeding time and by inhibiting thrombin formation [7]. Indirect evidence of the possible involvement of the coagulation cascade in CIU came from the observation that the proportion of skin test-positive patients rises substantially if autologous plasma is

injected instead of autologous serum [8].

D-dimer is a breakdown product produced by the degradation of cross linked fibrin by the plasmin due to any etiology [9]. Also, it is produced in all situations in which coagulation and fibrinolysis are activated [10]. The absence of D-dimer implies that thrombosis is not occurring and negative D-dimer assays have an important role in excluding any diagnosis of coagulation [11]. It was found that D-dimer levels are higher in patients with severe exacerbation of CIU but whether this activation is the cause of CIU or an amplification system is still a matter of debate [12]. The aim of this study is to compare plasma D-dimer levels in patients with CIU and in those with CU of known cause trying to resolve the above mentioned debate.

METHODS

This case control study included thirty CU patients (16 females and 14 males) recruited from the outpatient clinics of Dermatology; and Allergy and Immunology, Faculty of Medicine, AinShams University. Their ages ranged from 19 to 48 years. Ten patients were suffering from CU of known cause and twenty patients were suffering from CIU, with various degrees of severity. The diagnosis was made on clinical grounds. Doubtful cases were not included in the

study. Urticarial severity was estimated according to the number of wheals as follows [12]:

1–10 small (<3 cm in diameter) wheals: grade 1 (slight).

10–50 small wheals (<3 cm in diameter) or 1–10 large wheals (>3 cm in diameter): grade 2 (moderate).

>50 small wheals or >10 large wheals (>3 cm in diameter): grade 3 (severe).

Virtually all the body covered with wheals with angioedema: grade 4 (very severe).

Patients and controls were subjected to full history taking, general examination, dermatological examination and other investigations as required to exclude possible causes of CU such as prick test, neutrophil phagocytosis inhibition test (PIT), erythrocyte sedimentation rate (ESR), complete blood count (CBC) and thyroid function tests. Two millilitres of blood were obtained from patients (before and after remission) and from controls to measure plasma D-dimer levels by ELISA (Zymutest D-dimer; Hyphen BioMed, France). Statistical analysis of the results was performed using SPSS program version 14.

RESULTS

There was no statistically significant difference as regards gender and age between cases and controls. Also, there was no statistically significant difference as regards gender, age and duration of the disease between CIU patients and patients with CU of a known cause and between patients with different severity grades. There was no significant correlation between plasma D-dimer level and age of studied patients, $r=-0.021$, $p>0.05$) or between it and duration of the disease ($r=0.22$, $p>0.05$).

The levels of plasma D-dimer in all patients, CIU patients, CU patients of known cause and controls are shown in table 1. The levels was statistically significantly higher in all patients compared to controls ($p<0.001$) (figure 1) but no statistically significant difference could be detected between its levels in CIU and CU of known cause ($p>0.05$) (figure 2).

The levels of plasma D-dimer regarding different severity grades in CIU patients and CU patients of known cause are shown in table 2. In both groups, the levels were statistically significantly higher in very severe cases compared with mild cases ($p<0.001$). Also, there was a significant difference between mild and moderate, mild and severe, and moderate and very severe cases ($p<0.005$). Overall, there was a

statistically significant difference between the 4 severity groups as regards mean D-dimer level with significantly higher levels among patients with very severe urticaria (figure 3).

The levels of plasma D-dimer after treatment ranged from 31 to 311 ng/ml with a mean of 132.47 ng/ml (± 79.61) and a median of 103 ng/ml. The levels of plasma D-dimer was statistically significantly higher in all patients before treatment compared to after treatment levels ($p<0.001$). In each severity group, there was a statistically significant decrease as regards the plasma D-dimer levels after than before treatment ($p<0.05$) (figure 4).

Figure 1

Table 1. Summary of data of patients and control group

	Total number of patients	Idiopathic urticaria	Urticaria of a known cause	Control group
Number of patients	30	20	10	10
Gender	Female	16	12	4
	Male	14	8	6
Age(year; mean \pm SD)	30.93 \pm 8.88	31.2 \pm 9.03	30.4 \pm 9	30.1 \pm 8.25
Duration of disease(year; mean \pm SD)	3.75 \pm 2.82	3.8 \pm 2.8	3.65 \pm 3	—
D-dimer before treatment (mean \pm SD)	293.73 \pm 136.91	302.9 \pm 146.5	275.4 \pm 120.54	64.9 \pm 17.99
D-dimer before treatment (median)	295	293	302	64
D-dimer after treatment (mean \pm SD)	132.47 \pm 79.61	149.4 \pm 88.06	98.6 \pm 46.3	—
D-dimer after treatment (median)	103	107	99	—

Figure 2

Table 2. Summary of data of patients with different severity grades in CIU and CU of a known cause

	Idiopathic urticaria				Urticaria of known cause			
	Mild	Moderate	Severe	Very severe	Mild	Moderate	Severe	Very severe
Number of patients	6	6	4	4	3	3	2	2
Gender	Female	3	4	2	3	1	1	1
	Male	3	2	2	1	2	2	1
Age(year; mean \pm SD)	31 \pm 9.51	30.67 \pm 8.73	31.75 \pm 12.45	31.75 \pm 9.11	31 \pm 14.8	30 \pm 7.81	30.5 \pm 6.36	30 \pm 11.31
Duration of disease(year; mean \pm SD)	3.83 \pm 4.59	3.75 \pm 1.79	3.88 \pm 2.25	3.75 \pm 2.06	3.83 \pm 4.54	3.33 \pm 4.07	3.75 \pm 0.35	3.75 \pm 3
D-dimer before treatment (mean \pm SD)	182.5 \pm 84.4	289.83 \pm 21.54	308.75 \pm 31.86	497.25 \pm 206.23	136 \pm 123.85	294.67 \pm 24.54	325 \pm 19.8	406 \pm 7.07
D-dimer before treatment (median)	220	293	320	425	65	293	325	406
D-dimer after treatment (mean \pm SD)	75.83 \pm 26.32	152.5 \pm 90.21	189.75 \pm 74.08	214.75 \pm 100.98	55 \pm 22.75	110 \pm 12.29	88 \pm 12.73	157.5 \pm 67.18
D-dimer after treatment (median)	84	109.5	220	227	45	105	88	157.5

Figure 3

Figure 1. Comparison between cases and controls as regards plasma D-dimer levels.

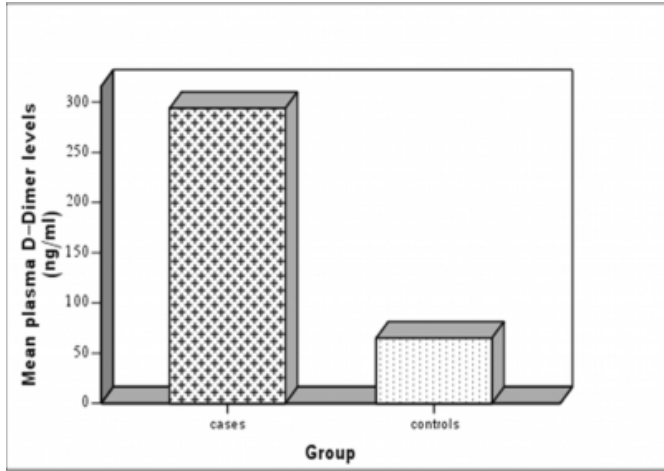


Figure 4

Figure 2. Comparison between the 2 groups and controls as regards plasma D- dimer levels.

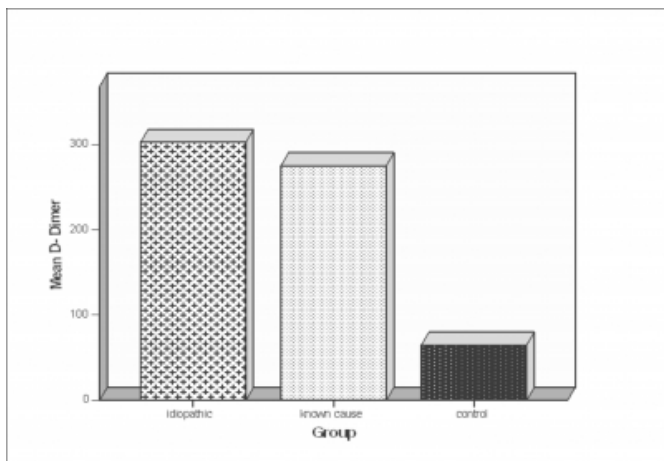


Figure 5

Figure 3. Comparison between the 4 severity grades in both groups as regards plasma D-dimer level before and after treatment

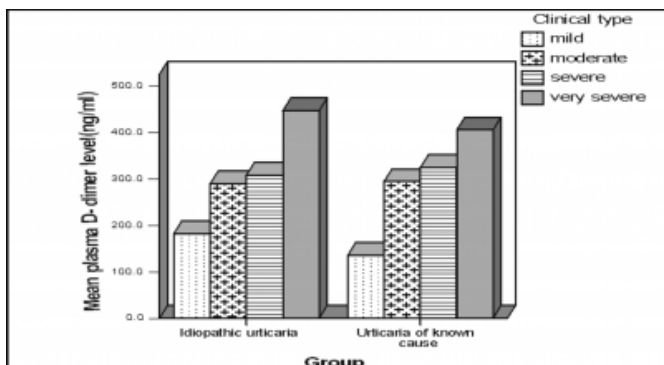
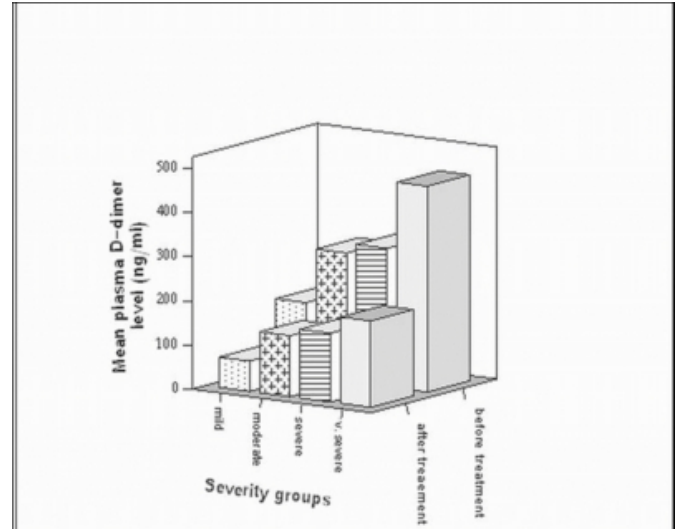


Figure 6

Figure 4. Comparison between the 4 severity grades in both groups as regard plasma D-dimer level.



DISCUSSION

The sequence of etiologic and pathogenic activation of the coagulation cascade in chronic idiopathic urticaria is still insufficiently defined. If autoantibodies, complement, and mast cell-derived factors such as histamine, tryptase, and/or different cytokines are responsible for the activation of endothelial cells causing tissue factor expression, then the observed activation of the extrinsic coagulation pathway would be a secondary consequence of urticaria, and thrombin might act as the final actor amplifying the increase in vascular permeability observed in this disease [14].

Results of our study showed a significantly higher elevation in the plasma level of D-dimer in all CIU patients compared to healthy controls. Similar results were reported by Asero et al. (2007) and Asero et al. (2008) [12, 13]. This could be explained by an activation of coagulation cascade via the tissue factor pathway with the involvement of inflammatory cells, leading to the formation of thrombin which might be responsible for generating C5a and increasing vascular permeability. On the other hand, the excess in fibrin formation could be counter-balanced by an enhanced fibrinolysis, as suggested by the increase in D-dimer levels [14]. In the current study, there was no significant correlation between plasma D-dimer and gender, age or duration of the studied patients or controls. This highly suggests that CIU is the main factor affecting plasma D-dimer levels.

Zajac and co-workers (2007) on the other hand, could not find significant differences in plasma concentrations of D-

dimer between the patients and the control subjects ($p > 0.05$) [15].

In our study higher levels of D-dimer were detected in relation to the severity of CIU that a highly significant difference ($p > 0.001$) was detected between severe and mild cases. Similar results were reported by Asero et al (2008) who explained that severe exacerbations of CIU are associated with a strong activation of coagulation cascade and fibrinolysis [12].

Plasma D-dimer levels were elevated in all CU patients with no significant difference between patients with CIU and patients with CU of a known cause ($p > 0.05$). This favors elevated D-dimer levels as an aggravating factor not a cause in CU. In fact, there are several pieces of evidence denoting the activation of the extrinsic pathway of coagulation cascade leading to fibrinolysis, which is indicated by elevated plasma D-dimer levels in CU. An indirect evidence of the possible involvement of the coagulation cascade in CU came from the observation that the proportion of skin test-positive patients rises substantially if autologous plasma is injected instead of autologous serum (about 80% vs. 50%) [8]. Elevated plasma levels of prothrombin fragment F1+2, suggesting thrombin generation were also detected in CU patients [8].

Asero et al. (2007) [13] in completion to their previous study, measured prothrombin fragment F1+2 and D-dimer in relation to disease severity and found that this is the result of activation of the tissue factor pathway of coagulation cascade. Furthermore, in outpatients with slight to moderate CU, mean D-dimer plasma levels were significantly higher than in a group of age- and sex-matched normal controls, although only in very few cases D-dimer levels exceeded the normal range [13].

Studies on animal models showed that thrombin increases vascular permeability both directly, acting on endothelial cells [16] and indirectly by inducing release of proinflammatory mediators by mast cells [17] and generates C5a in the absence of C3, thus bypassing the whole first part of the complement cascade [18].

we followed up all 30 patients after complete remission of symptoms by treatment which included steroids, antihistamines and desensitization therapy. There was a significant dramatic drop of plasma D-dimer levels compared to those during the acute exacerbation of the disease ($p < 0.001$). Similarly, Asero et al. (2008) had the

opportunity to measure plasma levels of D-dimer during an episode of severe exacerbation of the disease and after remission in only one patient and detected the same significant decrease [12].

In conclusion, the present work provides further evidence for the elevation of D-dimer, as a clue of activated coagulation cascade, in the circulation of CU patients. Its concentration increases with increased disease severity reverting the lower levels after complete remission of symptoms. Activated tissue coagulation pathway may be an aggravating or pathogenic factor in any type in CU not a specific cause in CIU. The possible role of anticoagulant therapy in decreasing severity of the disease and preventing worsening of symptoms is suggested and need further controlled studies to evaluate its efficacy.

References

1. Grattan CE, Sabroe RA, Greaves MW. Chronic urticaria. *J Am Acad Dermatol* 2002; 46: 645–657. PMID: 12004303
2. Champion RH. A practical approach to urticarial syndromes—a dermatologist's view. *Clin Exp Allergy* 1990; 20: 21–4. PMID: 2192784
3. Sabroe RA, Seed PT, Francis DM, Barr RM, Black AK, Greaves MW. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-Fc γ RI or anti-IgE autoantibodies. *J Am Acad Dermatol* 1999; 40: 443–50. PMID: 10071316
4. Tong LJ, Balakrishnan G, Kochan JP, Kinet JP, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997; 99: 461–465. PMID: 9111489
5. Valent P, Baghestanian M, Bankl HC, Sillaber C, Sperr WR, Wojta J, Binder BR, Lechner K. New aspects in thrombosis research: possible role of mast cells as profibrinolytic and antithrombotic cells. *Thromb Haemost* 2002; 87: 786–790. PMID: 12038777
6. Sillaber C, Baghestanian M, Bevec D, Willheim M, Agis H, Kapiotis S, Füreder W, Bankl HC, Kiener HP, Speiser W, Binder BR, Lechner K, Valent P. The mast cell as site of tissue-type plasminogen activator expression and fibrinolysis. *J Immunol* 1999; 162: 1032–1041. PMID: 9916730
7. Kauhanen P, Kovanen PT, Reunala T, Lassila R. Effects of skin mast cells on bleeding time and coagulation activation at the site of platelet plug formation. *Thromb Haemost* 1998; 79: 843–847. PMID: 9569202
8. 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: 1113–1117. PMID: 16675340
9. Freyburger G, Trillaud H, Labrousse S, Gauthier P, Javorschi S, Bernard P, Grenier N. D-dimer strategy in thrombosis exclusion—a gold standard study in 100 patients suspected of deep venous thrombosis or pulmonary embolism: 8 DD methods compared. *Thromb Haemost* 1998; 79: 32–7. PMID: 9459318
10. Goldstien MN, Kollef MH, Ward S, Gage BF. The impact of the introduction of rapid D-dimer assay on the diagnosis evaluation of suspected pulmonary embolism.

Arch Intern med 2001; 161: 567-71. PMID: 11252116

11. Keeling DM, Mackiel J, Moody A, Watson HG. The diagnosis of deep venous thrombosis in symptomatic out-patients and the potential assessment of D-dimer assay to reduce need for diagnostic imaging. *Br J Haematol* 2004; 124: 15-25. PMID: 14675404

12. Asero R, Riboldi P, Tedeschi A, cugno M, Griffini S, Bonanni E. Severe chronic urticaria is associated with elevated plasma levels of D-dimer. *Allergy* 2008; 63(2): 176-180. PMID: 17961199

13. Asero R, Tedeschi A, Coppola R, Griffini S, Paparella P, Riboldi P. Activation of the tissue pathway of blood coagulation in patients with chronic urticaria. *J Allergy Clin Immunol* 2007; 119: 705-710. PMID: 17204316

14. Asero R, Riboldi P, Tedeschi A, cugno M, Meroni P. Chronic urticaria: A disease at a crossroad between autoimmunity and coagulation. *Autoimmunity Rev* 2007; 7(1): 71-76. PMID: 17967729

15. Kasperska-Zajac A, Brzoza Z, Rogala B. Blood urokinase plasminogen activator system in chronic urticaria. *Arch Dermatol Res* 2007; 298: 409-411. PMID: 17102952

16. Nobe K, Sone T, Paul RJ, Honda K. Thrombin-induced force development in vascular endothelial cells: contribution to alteration of permeability mediated by calcium-dependent and -independent pathways. *J Pharmacol Sci* 2005; 99: 252-263. PMID: 16272788

17. Vliagoftis H. Thrombin induces mast cell adhesion to fibronectin: evidence for the involvement of protease-activated Receptor-1. *J Immunol* 2002; 169: 4551- 4558. PMID: 12370392

18. Huber-Lang M, Sarma JV, Zetoune FS, Rittirsch D, Neff TA, McGuire SR, Lambris JD, Warner RL, Flierl MA, Hoesel LM, Gebhard F, Younger JG, Drouin SM, Wetsel RA, Ward PA. Generation of C5a in the absence of C3: A new complement activation pathway. *Nat Med* 2006 ;12: 682-687. PMID: 16715088

Author Information

Nader F Ragab, MD

Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Ainshams University, Cairo-Egypt

Samar A Salem, MD

Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Ainshams University, Cairo-Egypt

Nelly M Hussein, M.B., B.Ch

Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Ainshams University, Cairo-Egypt