



## Original Research Article

## Evaluation of D-dimer levels as a marker of chronic refractory urticaria and its correlation with disease severity

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## ABSTRACT

**Background:** Chronic idiopathic urticaria (CIU) is very well managed by second-generation antihistamines in the majority of the cases but in a certain subset of patients symptoms persist despite their use. A deeper dig into disease pathogenesis will open new treatment options and better patient management.

**Objectives:** To evaluate D-Dimer as an anti-histaminic resistant chronic urticaria marker and its correlation with disease severity.

**Materials and Methods:** Forty chronic urticaria patients attending skin OPD were enrolled and divided into 2 groups of 20 patients each according to response to antihistamines. D-dimer levels were done in each patient.

**Statistical analysis used:** Unpaired t-test was used for assessing two groups and Pearsons correlation coefficient was used to find correlation between D-Dimer levels and Urticaria activity score over 7 days (UAS-7).Result- D-dimer levels were significantly higher in group 1(chronic refractory urticaria) as compared to group 2(chronic urticaria) and there is a positive correlation between D-dimer levels and urticaria activity score (UAS7).

**Conclusion:** Newer insights into alternative pathomechanism of chronic urticaria will open up new treatment options for treatment-resistant cases, this will lead to better patient management and improvement in quality of life.

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### 1. Introduction

Chronic urticaria (CU) is a skin disorder characterized by recurrent eruption of itchy, short-lived wheals and flares, sometimes associated with angioedema, for more than 6 weeks duration. Chronic urticaria can affect 1% of the general population at some point in life.<sup>1</sup> Without any identifiable causes after detailed investigations, it is labeled as Chronic idiopathic urticaria (CIU). In one-fourth of the patients, autoimmunity is involved in the pathogenesis.<sup>1,2</sup>

Studies done by Asero et al. showed that in a certain subset of chronic urticaria patients, there is activation

of a coagulation cascade resulting in the conversion of prothrombin to thrombin.<sup>3,4</sup> Thrombin is capable of inducing edema by increasing vascular permeability and stimulating mast cell degranulation.

The majority of the patients respond well to second-generation antihistamines, but still, a certain subset of patients do not respond to a four-fold increase in the dose of antihistamines and are labeled as chronic refractory urticaria (CRU).

Asero et al. found that baseline D-Dimer levels were significantly elevated in patients not responding to standard anti-histaminic therapy.<sup>5</sup>

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There are a limited number of studies evaluating D-dimer as a biomarker of chronic refractory urticaria.

The purpose of this study was to evaluate D-dimer as a potential biomarker of chronic refractory urticaria which will result in better understanding and management of chronic urticaria patients with high urticaria severity scores over 7 days (UAS7).

## 2. Materials and Methods

This was an observational study conducted at the Department of Dermatology in a tertiary care hospital in North India. The study protocol was reviewed and approved by the Institutional Ethics Committee (GMC/IEC/22/TK57). (Figure 1)

Forty patients of urticaria attending skin OPD were enrolled after screening with proper inclusion and exclusion criteria and were divided into two groups chronic refractory urticaria (group 1) and other chronic idiopathic urticaria (group 2) based on response to antihistamines.

Patients in the age group 18-50 years were included in the study. Patients with physical urticaria, on medications like acetylsalicylic acid, clopidogrel, warfarin, or heparin, having concurrent inflammatory infection, asthma, allergic rhinitis, and atopic dermatitis and children below 18 years of age were excluded from the study.

Written informed consent was taken from each patient. Detailed history and general physical examination of every enrolled patient were done and recorded. Antihistamines were stopped for 5 days and urticaria activity score for 7 days (UAS7) was recorded in each patient. (Table 1)

Relevant laboratory investigations were done. D-dimer levels were done using ELISA. Values of D-Dimer above 0.5 microgram/milliliter fibrinogen equivalent units ( $\mu$ /ml FEU) were considered raised.

The data obtained was statistically evaluated using Statistical Package for Social Sciences (SPSS) version 21.0. The study groups were evaluated using an unpaired t-test and correlated using a Chi-Square test. The Pearson Correlation coefficient was used to assess the association between various parameters. P value below 0.05 was considered statistically significant. The correlation was significant at the 0.01 level (2-tailed).

## 3. Results

The study enrolled 40 patients – 20 in each group. Mean age in both groups was comparable ( $32 \pm 8.6$  in group 1 and  $34 \pm 11.2$  in group 2) (Table 2). The sex distribution is the same in both groups (F=14, M=6).

The mean duration of the disease is slightly higher in group 1 ( $3.3 \pm 4.7$  years) as compared to group 2 ( $1.2 \pm 1.07$  years) (Table 2). In both groups, the majority of the patients were homemakers by occupation.

All patients in group 1 were presented clinically with wheals whereas 10% (N=2) in group 2 had associated dermographism.

Itching was the sole symptom in all the patients in group 1 and 90 % (N=18) in group 2. For the remaining 10% (N=2), one has an associated burning sensation and the other has angioedema.

Aggravation of the disease around menstruation was reported in three patients.

Most of the patients had no associated complaints except for three. One had allergic rhinitis, another was hypertensive, and one had associated joint pains.

The one with joint pains had raised ESR (25mm/hr). Anti-nuclear antibodies, rheumatoid factor, and D-dimer levels were normal.

The urticaria activity scores (UAS7) were significantly higher ( $p=0.04$ ) in group 1 ( $28.5 \pm 8.98$ ) as compared to group 2 ( $22.65 \pm 9.17$ ) (Table 2). Routine laboratory investigations were normal in both groups except for slightly raised serum Ig. E levels in a few patients (5/40). Two patients of group 1 with raised D-dimers had unusually high serum Ig. E levels (2500 IU/ml and 3912 IU/ml). The thyroid profile was within normal limits in all the patients.

Patients of chronic refractory urticaria showed significantly higher ( $p=0.012$ ) D-dimer levels ( $2.3 \pm 3.10$ ) in comparison with patients of chronic urticaria ( $1.05 \pm 0.99$ ) (Table 2).

There is a statistically significant correlation between UAS7 and D-dimer levels in both groups ( $r=0.44$ ) (Figure 2).

## 4. Discussion

According to international EAACI/ GA<sup>2</sup>LEN/ EuroGuiDerm/ APAAACI guidelines, second-generation antihistamines are the first line in the management of chronic urticaria and are recommended up to 4X dose.<sup>6</sup> Majority of the patients respond very well to this but a subset of chronic urticaria patients do not respond even to 4X dose and frequently require short course of steroids. This subset is labeled as chronic refractory urticaria. In most of the patients, the cause of urticaria is idiopathic. Autoimmunity as the cause of urticaria is a relatively new concept and these patients either have autoantibodies to serum immunoglobulin E (IgE) or too high-affinity IgE receptors on the mast cells.<sup>1,2</sup>

The mean age of the study population in both groups ( $32 \pm 8.6$  in group 1 and  $34 \pm 11.2$  in group 2) is slightly less than in studies done by Triwongwanat et al. and Chauhan et al. in which the mean age was 38.8 years and  $36.12 \pm 10.9$  years respectively.<sup>5,7</sup> This slight difference can be attributed to the small sample size in our study.

Female patients constituted 70% of the study population. Our results are consistent with studies done by Triwongwanat et al., Chauhan et al., and Asero et al.

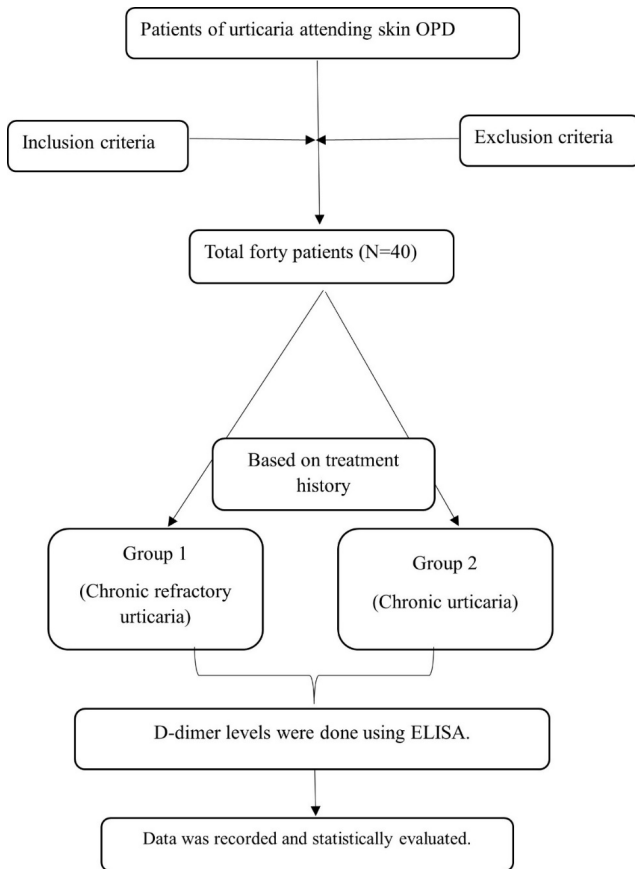
**Table 1:** Urticaria Severity Score

	<b>Wheals</b>	<b>Pruritus</b>
Score 0	none	none
Score 1 (Mild)	<20 wheals/24 hrs	Present but not annoying or troublesome
Score 2 (Moderate)	20-50 wheals/24 hrs	Troublesome but does not interfere with normal daily activity or sleep
Score 3 (Severe)	>50 wheals/ 24 hrs or large confluent areas of wheals	Severe pruritus interfering with normal daily activity or sleep

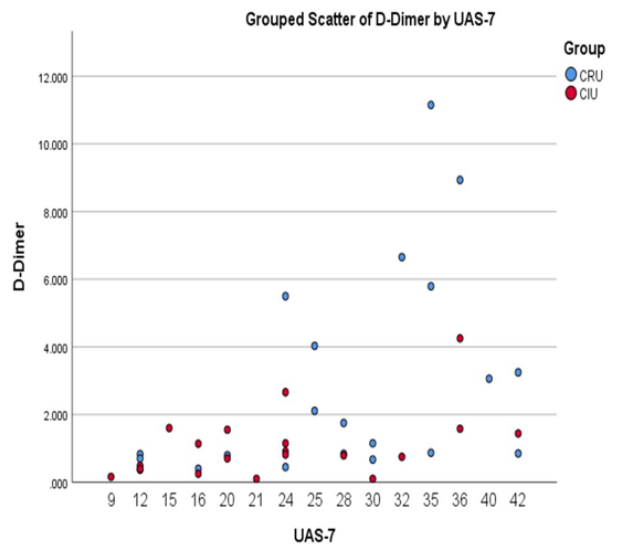
UAS7-aum of score (wheals score + pruritus score) for 7 days for a maximum of 42.

**Table 2:** Shows mean D-dimer levels, UAS7, Duration and age in group 1 and group 2

Variables	Group	Number of patients	Mean	Standard Deviation	Standard Error Mean
D-Dimer	CRU	20	2.988	3.106	0.694
	CIU	20	1.059	0.990	0.221
UAS	CRU	20	28.55	8.988	2.010
	CIU	20	22.65	9.172	2.051
Duration	CRU	20	3.355	4.772	1.067
	CIU	20	1.283	1.077	0.240
Age	CRU	20	31.95	8.648	1.934
	CIU	20	34.25	11.397	2.548



**Figure 1:** Showing the study design.



**Figure 2:** Showing positive correlation between D-dimer levels and Urticaria activity scores over 7 days (UAS-7).

In their studies, females constituted 75%, 70%, and 75% of total cases respectively. This female preponderance can be explained by the fact that chronic urticaria is twice as common in females as men owing to hormonal influences in females.<sup>5,7,8</sup>

In favor of hormonal influences on chronic urticaria, premenstrual aggravation of the disease was seen in three of our patients. Sex hormones are known to modulate immune and inflammatory cell functions, including mast cell secretion, and are regarded as responsible for gender and menstrual cycle phase-associated differential susceptibility

and severity of some autoimmune and inflammatory diseases. Hormonal fluctuations around menstruation especially progesterone have been attributed to the flare-up around menstruation. Autoimmunity in the form of progesterone hypersensitivity syndrome has been found in a few studies.<sup>9</sup> Study by Kasperska et al. found lower serum dehydroepiandrosterone sulfate (DHEA-S) concentration in patients with chronic urticaria.<sup>10</sup>

Dermographism was seen in one of our patients (1/40 patients-2.5%). The prevalence of dermographism in patients of chronic idiopathic urticaria was found to be 3.8% in a retrospective study done by Kulthanan et al. on 450 cases. Prevalence in our study is slightly lower, and this could be attributed to the small sample size in our study.<sup>11</sup>

In our study, one patient had associated allergic rhinitis. Studies by Isik et al. and Dziewa et al. reported that the prevalence of allergic rhinitis and other allergic conditions like bronchial asthma and nasal polyps are higher in patients with chronic urticaria. This association could be attributed to increased sensitivity to allergens in both cases. The presence of allergic rhinitis does not alter the response to antihistamines.<sup>12,13</sup>

Chang et al. and Nebiolo et al. in their studies found that hypertension is associated with an extended duration of disease and there is a higher risk of future hypertension in patients with chronic urticaria.<sup>14,15</sup> Not much research has been done in the past regarding this association. Recently, activation of the coagulation cascade due to vessel wall injury in the early stages of hypertension has been proposed as a probable mechanism. Alternation in the fibrinolytic-hemostatic balance predisposes to a procoagulant state and raised prothrombin fragments and D-dimer levels.<sup>16,17</sup> Concerning association with hypertension, one of the patients of CRU has a history of hypertension, however, D-dimer levels were normal.

Joint pains were associated with chronic urticaria in one of our patients. Doong et al. in their study documented that joint pains were the most commonly associated systemic symptom in patients with chronic urticaria (57/103 patients -53% of patients), but further cause evaluation of joint pains was not done in this study.<sup>18</sup> Joint pains in chronic urticaria could be due to inflammatory diseases like rheumatoid arthritis, gout, or autoimmune diseases or could be idiopathic. In our study, the patient had both ANA and RA factor was negative, but ESR was raised, pointing towards underlying inflammation.

Elevated S.Ig E levels of more than 1000IU/ml were seen in two CRU patients with raised D-dimer levels. In a study by Altrichter et al. found that higher serum Ig E levels were associated with increased disease severity and longer duration of disease.<sup>19</sup> In accordance with this study, our study showed that CRU was very severe in both patients with very high S. IgE levels (UAS7-42 and 28).

D-dimers are the marker of activation of coagulation cascade, and they are commonly elevated in deep venous thrombosis, and coagulation defects like disseminated intravascular coagulation. Apart from this, D-dimer is an inflammatory marker like CRP and is elevated in inflammatory and autoimmune diseases. Various studies done by Asero et al. found that D-dimers are raised in patients with chronic urticaria.<sup>3,4</sup>

In our study, D-dimer levels are elevated both in patients of chronic urticaria (65% patients) and chronic refractory urticaria (90% patients), but the levels are significantly higher in CRU patients ( $2.3 \pm 3.10 \mu\text{g/ml}$  FEU). Our results are comparable to a study done by Asero et al. in which baseline D-Dimer levels were significantly elevated in patients not responding to standard antihistamine therapy ( $0.98$  to  $2.49 \mu\text{g/ml}$  FEU) and in these patients, good clinical response is seen with treatment with anti-coagulants and anti-fibrinolytics like tranexamic acid.<sup>8</sup>

The urticaria activity score (UAS7) was significantly higher ( $p=0.04$ ) in group 1 ( $28.5 \pm 8.98$ ) as compared to group 2 ( $22.65 \pm 9.17$ ). This is in concordance with a study by Chauhan et al., in which UAS 7 was more in patients with elevated D-dimer levels (between 16-42) than in controls.<sup>7</sup>

Consistent with the study by Triwongwaranat et al., our study found a positive correlation between plasma D-dimer levels and UAS7, and it indicates increased activation of the coagulation cascade in these patients, which can be the underlying cause for unresponsiveness to treatment.<sup>5</sup>

Ditto et al. showed a good response to hydroxychloroquine in the management of steroid-dependent chronic urticaria.<sup>20</sup> In our study, we put one patient of CRU with raised D-dimer levels on hydroxychloroquine 200mg twice a day. Patients showed excellent response by 8 weeks and D-dimer levels came to normal by 18 weeks. Our study lacks complete follow-up of the patient. Longer duration follow-ups are required to know the remission period and relapse rates after the stoppage of treatment.

## 5. Conclusion

D-Dimer levels can be used as a screening tool for suspected anti-histaminic resistance in patients of chronic urticaria and can be used for monitoring the response to therapy with alternative agents. Newer insights into disease pathogenesis will lead to a new armamentarium of treatment modalities and hence better patient management. Further research should be undertaken.

## 6. Limitations of Study

1. Small sample size.
2. Follow-ups were lacking in our study.

## 7. Source of Funding

None.

## 8. Conflict of Interest

None.

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