



EVALUATION OF D-DIMER SERUM LEVELS AMONG PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA AND ITS CORRELATION WITH DISEASE SEVERITY .

Dr. Aditi Jaiswal*

Department Of Dermatology Venereology and Leprosy.*Corresponding Author

Dr. Kiran Godse

Dr. DY Patil Medical College and hospital Navi Mumbai

ABSTRACT

Aims: To evaluate D-Dimer serum levels in patients with chronic urticaria and its correlation with disease activity.

Settings and Design: Single centre Cross sectional prospective observational age & sex matched case-control study at Dermatology OPD of a tertiary referral centre.

Methods and Material: This study was conducted from January 2018 to June 2019. We included 33 patients with CU and 30 controls . They were recruited from urticaria clinic. All cases were subjected to history taking, general and dermatological examination. The serum levels of D-Dimer were measured by Semiquantitative, immunofiltration kits.

Statistical analysis: Data was analysed by Statistical Package for Social Sciences (SPSS) version 21.0. Tests used were Independent t test/Mann-Whitney Test, Chi-Square test/Fisher's Exact test, Spearman rank correlation coefficient, Kolmogorov-Smirnov test..

Results: Patients with active CU had elevated D-Dimer serum levels ($p < 0.0001$) when compared with the control group (papulo-squamous disorder). Of 33 CSU patients, D-dimer level was elevated in 19 patients (57.58%). There was statistically significant positive correlation between disease severity (UAS7) and plasma D-dimer level ($p < .0001$, $r = 0.935$).

Conclusions: This study showed elevated D-dimer levels in more than half of Indian patients with CSU. There was a positive correlation between plasma D-dimer levels and the severity of disease activity. Investigation for plasma D-dimer level may be an alternative objective way to evaluate disease severity in patients with CSU.

Limitations: Low sample size . Semi quantitative method was used instead of ELISA for D-Dimer .

KEYWORDS : D-Dimer, chronic urticaria, UAS7

INTRODUCTION:

Chronic urticaria (CU) is a widespread skin disease, characterised by the recurrence of transient wheals and itch for more than 6 week¹. Chronic urticaria has wide spectrum of clinical presentations and aetiologies² which includes mast cell activation^{3,4}, autoimmunity^{5,6}, auto reactivity⁷, basophil activation⁸. Besides all the above mechanisms, some part of the pathogenesis of CSU remains unclear. It was observed that the autologous plasma skin test (APST) was positive in some ASST-negative patients⁹ and that IgG depleted serums from CSU patients retained ability to induce a wheal-and-flare reaction upon intradermal injection¹⁰. Due to these evidences it was inferred that clotting cascade may be involved in pathogenesis of urticaria. It has been observed in studies that tissue factor expressed by eosinophils can induce activation of coagulation cascade which in turn generates thrombin which can increase vascular permeability both directly by acting on endothelial cells, and indirectly by inducing degranulation of mast cells¹¹ and also may activate protease activation receptor1 (PAR1) on mast cells¹². In severe CSU patients, the coagulation cascade activation via extrinsic pathway is so extensive that it produces an elevation of D-dimer¹³. A fibrin degradation product that is D-Dimer is generated following activation of the coagulation cascade and is a sign of fibrinolysis. D-Dimer has been found to be increased during urticaria exacerbations and normalises in remission. Moreover, it has been proposed as a biomarker of severity in CSU patients¹⁴.

To date, there is no data concerning D-dimer level in Indian patients with CSU. We aim to evaluate the levels of D-Dimer level in patients with CSU and to study the correlation between D-dimer level and the activity of disease in Indian patients.

SUBJECTS AND METHODS:

This study was initiated only after obtaining approval from institutional ethics committee. It was carried out on 33 CSU patients & 30 controls (patients with papulo-squamous disorder) from Urticaria clinic at a tertiary referral centre. On

the basis of the inclusion and exclusion criteria, the study population was screened and selected. Informed consent explained to the patients in their own language was obtained after which an information sheet was provided to the patients.

Inclusion criteria : All chronic spontaneous urticaria patients above 18 years, who are willing for the blood investigation with Urticaria activity score 7 (UAS7) > 12.

Exclusion criteria : Patients who had history of bleeding disorder, deep vein thrombosis, pulmonary embolism, physical urticaria, history of recent surgery, were on anticoagulants or Pregnant.

A detailed history was recorded from the patient which included onset and duration of the disease, angioedema. History of any aggravating factor such as food, drugs, exercise, comorbidities. A complete general examination, dermatological examination was performed for all patients.

Assessment of ideas activity : Urticaria Activity Score 7 (UAS 7) was calculated at the time of collection of blood. Urticaria Activity Score 7 is the daily documentation of combined score of severity of itch and number of wheals to determine disease activity. Maximum score for 7 day score is upto 42. (Table 1)¹⁵.

Table 1 : Urticaria activity score 7

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 hour)	Mild (present but not troublesome / or only at rest)
2	Moderate (20-50 wheals / 24 hours)	Moderate (troublesome but does not interfere with sleep)
3	Intense (> 50 wheals/ 24 hour)	Intense (severe pruritus which interferes with sleep)

D-Dimer evaluation:

2 ml of venous blood was collected under aseptic precaution in sodium citrate bulb during the period of disease activity for estimation. The sample was transported to the lab within 3 hours. The serum was centrifuged at 1500 G for 15 minutes. Then the platelet poor plasma was separated in another tube which underwent double spin. This sample was used for testing. D-dimer plasma level was measured by Semiquantitative, immunofiltration kits. The cut-off level is 500 ng/mL.

Statistical Analysis:

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. Statistical tests were applied as follows-

1. Quantitative variables were compared using Independent t test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups.
2. Qualitative variables were correlated using Chi-Square test/Fisher's Exact test.
3. Spearman rank correlation coefficient was used to assess the association of various parameters with D-dimer and UAS 7.

p value of <0.05 was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results:

The study included 22 (66.67%) females and 11 (33.33%) males their age ranging from 18 to 65 years with mean ± SD of 31.97 years ± 9.83 amongst CSU group. And control group had 17 (56.67%) female and 13 (43.33%) Males with mean ± SD of 36.3 ± 12.05. The disease duration ranged between 2 - 36 months with mean ± SD 9.27 ± 7.8 (Table 2)

Table 2: demographic data of subjects (n=63)

	Case		Control	
	Number	%	Number	%
Gender				
male	11	33.33	13	43.33
female	22	66.67	17	56.67
Age				
Min-max	18 - 65		18 - 65	
mean ± SD	31.97 ± 9.83		36.3 ± 12.05	
median	30		36.5	

Out of the 63 patients tested for D-Dimer, in patients with severe CSU, mean value of D-Dimer (697.12 ng/ml) largely exceeded from those found in control (129.87) giving significant p-value (0.0001) [Figure 1].

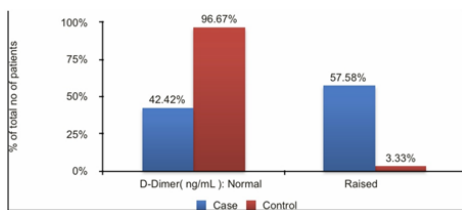


Figure 1: Distribution of cases & controls according to D-Dimer

Amongst the enrolled CSU cases, normal plasma D-dimer level was observed in (42.42%) and elevated plasma D-dimer

level was in (57.58 %). We observed a statistically significant positive correlation between UAS7 & D-dimer (p <.0001, r =0.935) [Figure 2].

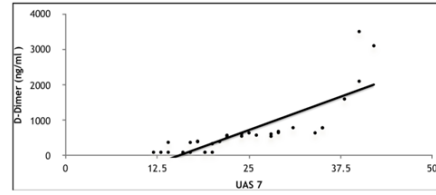


Figure 2: Correlation between UAS 7 & D-Dimer (ng/ml)

It was observed that the higher UAS7 i.e. 32-42 showed elevated D-Dimer in 99% patients. Whereas moderate severity urticaria (UAS7 12-30) showed 56% with normal Dimer and 44% with elevated D-Dimer. [Figure 3]

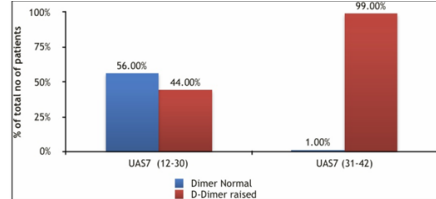


Figure 3: Distribution of cases depending on severity and D-Dimer

The mean age of elevated D-Dimer levels in patients of CSU is 32 years i.e common in 3rd decade with a female predominance. The average duration of disease in D-Dimer positive patients is 8 months. We also observed that as the duration increased D-Dimer levels reduced [Figure 4].

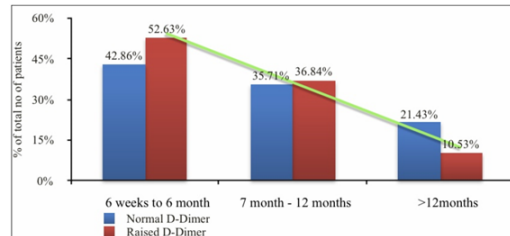


Figure 4: Correlation between Duration of the disease & D-Dimer levels (ng/ml)

Out of 33 patients in our study, 14 patients had either history of angio-oedema. Out of these 14 patients, 9 (64.28 %) showed raised D-Dimer and 5 (35.71 %) showed normal D-Dimer levels (Table 3). 2 patients of CSU had hypothyroidism and we observed that they had elevated D-Dimer levels. But no statistically significant correlation could be found between the two parameter.

Table 3 : Comparison between and angioedema and D-Dimer

	Angioedema present	Angioedema absent	P-value
D-Dimer Raised	9	10	0.503 (NS)
D-Dimer Normal	5	9	

DISCUSSION:

Urticaria is a common disease which has a negative impact on quality of life of the patients. The disease carries a significant emotional and economic burden on the patient¹⁶. In order to provide adequate treatment to the patients, the evaluation of disease severity and activity is essential. But there is no reliable biomarker for such evaluations and it solely depends on subjective description. The involvement of coagulation cascade in pathophysiology of urticaria was proposed in a few studies^{13,17}. The markers of thrombin generation and fibrinolysis was elevated in urticaria was noticed^{18,19}.

Epidemiologically, among the group with elevated D-Dimer, female outnumbered male which was similar to what is known^{14,20} with mean age being 32 years i.e common in 3rd decade. Out of 33 patients in our study, 14 patients had either history of angio-oedema or presented with it. Out of these 14 patients, 9 (64.28%) showed raised D-Dimer levels. In the study by Alwafa et al²¹ 32.5% and by Sabroe et al⁽²²⁾ 85% patients had a history of positive angioedema. 2 patients of CSU had hypothyroidism and we observed that they had elevated D-Dimer levels. But no statistically significant correlation could be found between the two parameters.

In this study we found normal plasma D-dimer level in (42.42%) of enrolled CSU patients and elevated plasma D-dimer level in (57.58%) of them. Previous studies showed increased D-Dimer level in 54.5% by Criado et al¹⁴, 37.5% by Alwafa et al²¹, Triwongwaranat et al²³ found elevated D-dimer levels in 48.3%, in 35% by Takahagi S¹⁸. Similar findings were also observed by Asero et al²⁴. The difference in observations may be due to difference in severity of patient selected.

Our study also showed the positive correlation between plasma D-dimer level and disease severity ($p < .0001$, $r = 0.935$). Similar correlation was also observed in few other studies^{23,24,25}. We observed that the patients with severe urticaria had mean level of D-Dimer (1047.1 ng/ml \pm 889.68) which largely exceeded those found in moderate urticaria (222.14 ng/ml \pm 147.17). Asero et al²⁴ also observed that median level in chronic urticaria exceeded from that in moderate urticaria and in controls. The coagulation cascade activation and fibrinolysis that is exaggerated in exacerbation decreases till it complete normalises during remission of CSU²⁴.

CONCLUSION :

This study showed elevated plasma D-dimer levels in more than half of Indian patients with CSU and there was a positive correlation between plasma D-dimer levels and the severity of disease activity. We would like to conclude by saying that plasma D-dimer levels may be an alternative objective way to evaluate disease severity in patients with CSU.

LIMITATIONS:

- Low sample size .
- Semi quantitative method was used instead of ELISA for D-Dimer .

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