

# Evaluation of D-dimer serum levels among patients with chronic urticaria, psoriasis and urticarial vasculitis\*

Avaliação dos níveis séricos de D-dímeros entre doentes com urticária crônica, psoríase e urticária vasculite

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**Abstract:** BACKGROUND: It has been demonstrated that neutrophils, eosinophils and monocytes, under appropriated stimulus, may express tissue factor and therefore, activate the extrinsic pathway of coagulation. We performed a transversal and case-control study of patients with chronic urticaria and patients with psoriasis, in our outpatient clinic to evaluate the production of D-dimer. OBJECTIVE: To evaluate D-dimer serum levels in patients with chronic urticaria and its possible correlation with disease activity. PATIENTS AND METHODS: The study was conducted from October 2010 until March 2011. We selected 37 consecutive patients from our Allergy Unit and Psoriasis Unit, and divided them into three groups for statistical analysis: (i) 12 patients with active chronic urticaria (CU); (ii) 10 patients with chronic urticaria under remission and (iii) 15 patients with psoriasis (a disease with skin inflammatory infiltrate constituted by neutrophils, lymphocytes and monocytes). Another five patients with urticarial vasculitis were allocated in our study, but not included in statistical analysis. The serum levels of D-dimer were measured by Enzyme Linked Fluorescent Assay (ELFA), and the result units were given in ng/ml FEU. RESULTS: Patients with active chronic urticaria had the highest serum levels of D-dimer ( $p < 0.01$ ), when compared to patients with CU under remission and the control group (patients with psoriasis). CONCLUSIONS: Patients with active chronic urticaria have higher serum levels of D-dimer, when compared to patients with chronic urticaria under remission and patients with psoriasis. We found elevated serum levels of D-dimer among patients with urticarial vasculitis.

Keywords: Angioedema; Psoriasis; Urticaria; Vasculitis; Vasculitis, leukocytoclastic, cutaneous

**Resumo:** FUNDAMENTOS: Tem sido demonstrado que os neutrófilos, eosinófilos e monócitos, sob estímulo apropriado, podem expressar fator tecidual e, portanto, ativar a via extrínseca da coagulação. Realizamos um estudo transversal e caso-controle de pacientes com urticária crônica e pacientes com psoríase em nosso ambulatório para avaliar a produção de dímero-D. OBJETIVO: Avaliar níveis de dímero-D em pacientes com urticária crônica e sua possível correlação com a atividade da doença. PACIENTES E MÉTODOS: O estudo foi conduzido de outubro de 2010 até março de 2011. Nós selecionamos 37 pacientes consecutivos da Unidade de Alergia e Unidade de Psoríase, divididos em três grupos para análise estatística: (i) 12 pacientes com urticária crônica ativa; (ii) 10 pacientes com urticária crônica em remissão e (iii) 15 pacientes com psoríase (uma doença com a pele infiltrado inflamatório constituído por neutrófilos, linfócitos e monócitos). Outros cinco pacientes com vasculite urticariforme foram alocados em nosso estudo, mas não incluídos na análise estatística. Os níveis séricos de D-dímero foram medidos por Enzyme Linked Fluorescent Assay (ELFA), e os resultados foram medidos em ng / ml FEU. RESULTADOS: Os pacientes com urticária crônica ativa tinham níveis séricos mais altos de dímero-D ( $p < 0,01$ ), quando comparados aos pacientes com urticária crônica em remissão e ao grupo controle (pacientes com psoríase). CONCLUSÕES: Os pacientes com urticária crônica ativa têm níveis séricos mais elevados de dímero-D, quando comparados aos pacientes com urticária crônica em remissão e aos pacientes com psoríase. Encontramos níveis elevados de dímero-D entre os pacientes com vasculite urticariforme.

Palavras-chave: Angioedema; Psoríase; Urticária; Vasculite; Vasculite leucocitoclástica cutânea

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## INTRODUCTION

Chronic urticaria (CU) has a wide spectrum of clinical presentations and possible etiologies.<sup>1-3</sup> The pathogenesis of CU includes immunological and non-immunological types and an idiopathic type. Moreover, it has been recently associated with the presence of histamine-releasing IgG autoantibodies, found in 50% of cases previously considered of unknown cause, which characterizes the autoimmune urticaria.<sup>4</sup> Urticaria is caused by degranulation of cutaneous mast cells and/or basophils. Degranulation releases potent vasoactive mediators that induce vasodilatation and increased capillary permeability, resulting in erythema and wheal formation. Itching and pain are caused by sensory nerve stimulation. The main vasoactive mediator is histamine, but there are other inflammatory mediators such as arachidonic acid metabolites, leukotrienes (LTC<sub>4</sub>, D<sub>4</sub> and E<sub>4</sub>), prostaglandin D<sub>2</sub>, serotonin, acetylcholine, platelet activating factor, heparin, codeine, anaphylatoxins C<sub>3</sub>, C<sub>5a</sub>, quinones and neurotransmitters released from cutaneous nerve endings.<sup>5</sup> Degranulation is related to immunological causes (IgE, immune complexes, complement dependent), non-immunological causes (pseudoallergic, infectious or due to direct action of agents released by mast cells) and idiopathic. One of the most important factors that induce degranulation of mast cells in chronic urticaria is the presence of histamine IgG releasing autoantibodies against  $\alpha$ -subunit IgE high affinity receptor (Fc $\epsilon$ RI $\alpha$ ) or against IgE, which has been demonstrated in 50% of patients with chronic idiopathic urticaria.<sup>6,7</sup>

Recent reports revealed that patients with CU show signs of thrombin generation and activation of the tissue factor pathway of the coagulation cascade.<sup>8</sup> D-dimer (DD) is a fibrin degradation product formed during the lysis of a thrombus. DD elevations are detected in plasma during the onset of thrombus formation and its elevation usually lasts about a week. For this reason, it is possible to find high levels of DD during increased fibrinolytic activity. It occurs in high concentrations in many clinical conditions, such as deep vein thrombosis and pulmonary embolism. It may be also be elevated in myocardial infarction, disseminated intravascular coagulation, pneumonia, heart failure, neoplasia, polytrauma or in patients undergoing surgery. Currently, elevated DD has also been associated with severity and activity of chronic urticaria.<sup>9,10</sup> The normal serum level of DD is less than 500 micrograms/litre. The serum levels of D-dimer were measured by Enzyme Linked Fluorescent Assay (ELFA), and the result units were given in ng/mL FEU – fibrinogen equivalent unit. A positive value was over 200 ng/mL FEU, with a negative result when the final value was less than that.

There are few reports about the relationship between DD levels and chronic urticaria and its role in this disease, which led us to make this work.

## PATIENTS AND METHODS

The study population comprised patients with chronic urticaria (more than 6 weeks of disease), attending our outpatient clinic (Allergy Unit) from October 2010 to March 2011. The inclusion criterion was the clinical and histopathologic diagnosis of chronic urticaria (CU) and exclusion criteria were the diagnosis of other diseases that could alter the coagulation cascade, or the use of anticoagulant therapy. The control population consisted of patients with psoriasis, from our outpatient clinic (Psoriasis Unit).

The design of this research was descriptive and transversal case-control. The first and second groups of patients with chronic urticaria that underwent d-dimer levels measurements were classified as: active (symptomatic) CU (12 patients) and CU under remission (10 patients). Fifteen volunteers with psoriasis constituted the third group.

The active CU group was defined as patients showing the presence of active cutaneous lesions as urticarial plaques, using hydroxyzine and loratadine. This group consisted of 12 patients, ten females and two males, with ages ranging from 24 to 69 years old, (mean age 37.5 years).

There were 10 patients in the CU group in remission (seven females and three males; aged between 28-49 years old, with mean age of 39.3 years). For remission criteria we established that the patients must have been without urticaria or angioedema lesions for a minimum period of 30 days and under treatment with antihistamines (hydroxyzine plus loratadine).

The control group was composed of 15 patients with psoriasis (seven females and eight males; range 28-53 years-old, mean age 42.4 years).

Five patients with chronic, active lesions resembling urticaria, with histopathologic findings that further revealed leukocytoclastic vasculitis, indicating the diagnosis of urticarial vasculitis, were also included as a separate group. We evaluated D-dimer serum levels in this group of patients. However we did not include these patients in the statistical analysis due to the small number of cases.

The serum levels of D-dimer were measured by Enzyme Linked Fluorescent Assay (ELFA), and the result was given in ng/mL FEU (fibrinogen equivalent unit).

## Study design and Statistical analysis

This is a transversal case-control study. The

potential differences in D-dimer levels between patients with active CU, compared with CU patients under remission and controls (patients with psoriasis) were calculated by application of Pearson's Chi-squared test.

**RESULTS**

All demographic data and D-dimer levels of the patients allocated in the study are described in table 1.

Elevated serum levels of D-dimer were found in 12 out of 22 patients with chronic the active urticaria (54.5%). The average D-dimer level was 869 ng/mL FEU; with the normal level being less than 500 ng/mL FEU. The remaining 10 patients with chronic urticaria under remission (45.5%) presented normal levels of DD (average 339 ng/mL FEU). In the control group (patients with psoriasis), only one patient exceeded the normal levels of the D-dimer, the others had normal levels with an average of 337 ng/mL FEU (Table 2).

After applying the tests of mean differences between patients with chronic urticaria with activity and under remission, the difference between the two groups was significant (p<0.01). Also, we calculated the odds ratio (OR) and it revealed that patients with chronic urticaria have OR = 18.0, for elevated D-dimer levels, compared with patients with psoriasis (Graph 1).

In three patients with urticarial vasculitis the disease was idiopathic during the study. One patient (case 4) had antiphospholipid antibodies and ANA positive. The D-dimer levels were elevated in all 5 patients with urticarial vasculitis (Table 3).

**DISCUSSION**

Skin reactivity to the intradermal injection of autologous serum (autologous serum skin test - ASST) and/or plasma (autologous plasma skin test - APST) has been proposed to identify chronic urticaria (CU) patients with an autoimmune or auto reactive disease.<sup>11</sup>

Immune-mediated inflammation and coagulation are strictly linked, and coagulation activation has been described in CU patients as shown by the elevations of plasma prothrombin fragment F1+2 and D-dimer.<sup>11</sup>

In CU, several investigators have demonstrated that the activation of coagulation is due to the involvement of eosinophils and a tissue factor pathway, with generation of thrombin potentially contributing to an increased vascular permeability. CU patients often present elevation of coagulation and fibrinolysis markers, such as prothrombin fragment F1+2 and D-dimer, which correlate with the disease severity.<sup>11</sup> Preliminary data indicate that anticoagulant treatment with heparin and warfarin may be effective in

**TABLE 1:** Demographic and D-dimer levels in all patients allocated in the study

Group of Patients	Patient number	Age (years)	Gender (F, female; M, male)	D-dimer level (ng/ml FEU)
Active Chronic Urticaria	1	36	F	1,400
	2	39	F	1,350
	3	69	F	1,016
	4	24	F	990
	5	29	M	800
	6	26	F	780
	7	34	F	760
	8	43	M	720
	9	36	F	708
	10	46	F	670
	11	26	F	650
	12	43	F	589
Chronic Urticaria under Remission	1	28	M	470
	2	44	F	470
	3	29	F	400
	4	38	F	380
	5	54	F	320
	6	45	F	310
	7	28	F	290
	8	38	M	280
	9	49	F	270
	10	40	M	200
Psoriasis	1	50	F	501
	2	52	M	420
	3	29	F	410
	4	32	M	400
	5	53	F	390
	6	44	F	380
	7	44	F	360
	8	49	M	330
	9	36	F	330
	10	37	M	320
	11	48	M	300
	12	48	M	250
	13	39	F	240
	14	28	M	220
	15	47	M	200
Urticarial Vasculitis	1	29	F	2,600
	2	48	F	1,200
	3	39	F	900
	4	59	M	890
	5	38	F	780

reducing the symptoms of CU. All these findings provide the rationale for proposing clinical trials on the use of anticoagulant drugs as adjuvant treatment in CU patients.<sup>8</sup>

Asero et al. correlated the presence of intense activity of the coagulation cascade with exacerbations of lesions in patients with chronic urticaria.<sup>11</sup> Recent reports revealed that patients with CU show signs of thrombin generation and activation of the tissue factor pathway of the coagulation cascade and autologous plasma skin tests score positive in as many as 95% of cases.<sup>12</sup> Moreover, CU patients showing positive response to ASST had plasma profile of the urokinase system-associated proteins, which was not markedly

different as compared with CU patients with negative ASST as well as healthy subjects, suggesting that systemic fibrinolysis may not be involved in chronic urticaria.<sup>13</sup>

In our study we also observed increased serum levels of D-dimer among patients with active CU and patients with urticarial vasculitis in all patients.

Mast cells, essential elements involved in the pathogenesis of CU, produce GM-CSF (granulocyte-macrophage colony-stimulating factor) and PAF (platelet-activating factor).<sup>14</sup> These factors stimulate resting eosinophils, inducing translocation of encrypted Tissue Factor (TF) to cytoplasmatic membrane, which will activate blood coagulation system.<sup>14</sup>

In CU, some authors have demonstrated that generation of thrombin could potentially be contributing to an increased vascular permeability, because thrombin may activate PAR-1 on endothelial cells, amplifying the inflammatory response in urticaria.<sup>8</sup> Mast cells express both PAR-1 and PAR-2. The thrombin generated may activate mast cells via PAR-1 and the complexes TF+FVIIa and FVa+FXa may activate these cells via PAR-2, amplifying the continuous activation of mast cells in CU.<sup>15</sup> (Figure 1).

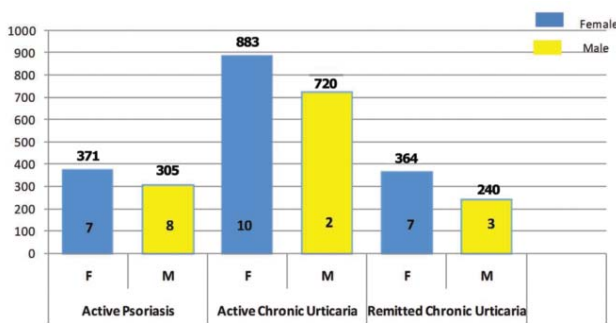
Our results are similar to those obtained by Asero et al, in that the use of D-dimer levels in the blood of patients with chronic urticaria could be a potential serum marker to withdraw antihistamine treatment, as there is a decrease in their values.<sup>12</sup> New prospective studies that include serum D-dimer level analysis in a larger number of patients with chronic urticaria, before and during treatment, are needed to accomplish this use.

To the best of our knowledge, the finding of elevated levels of d-dimer in the blood of patients with urticarial vasculitis has not been reported in the literature. Currently, it is known that tissue factor can be found encrypted (inactive) in the cytoplasm of various peripheral blood cell elements, such as monocytes, eosinophils, neutrophils and platelets.<sup>16</sup>

TABLE 2: Chronic Urticaria and D-dimer levels

	Chronic Urticaria		Psoriasis	
	N	%	N	%
Elevated D-dimer	12	54.5%	1	6.7%
Normal D-dimer	10	45.5%	14	93.3%
Total	22	100.0%	15	100.0%
OR = 18.0	p < 0.01			

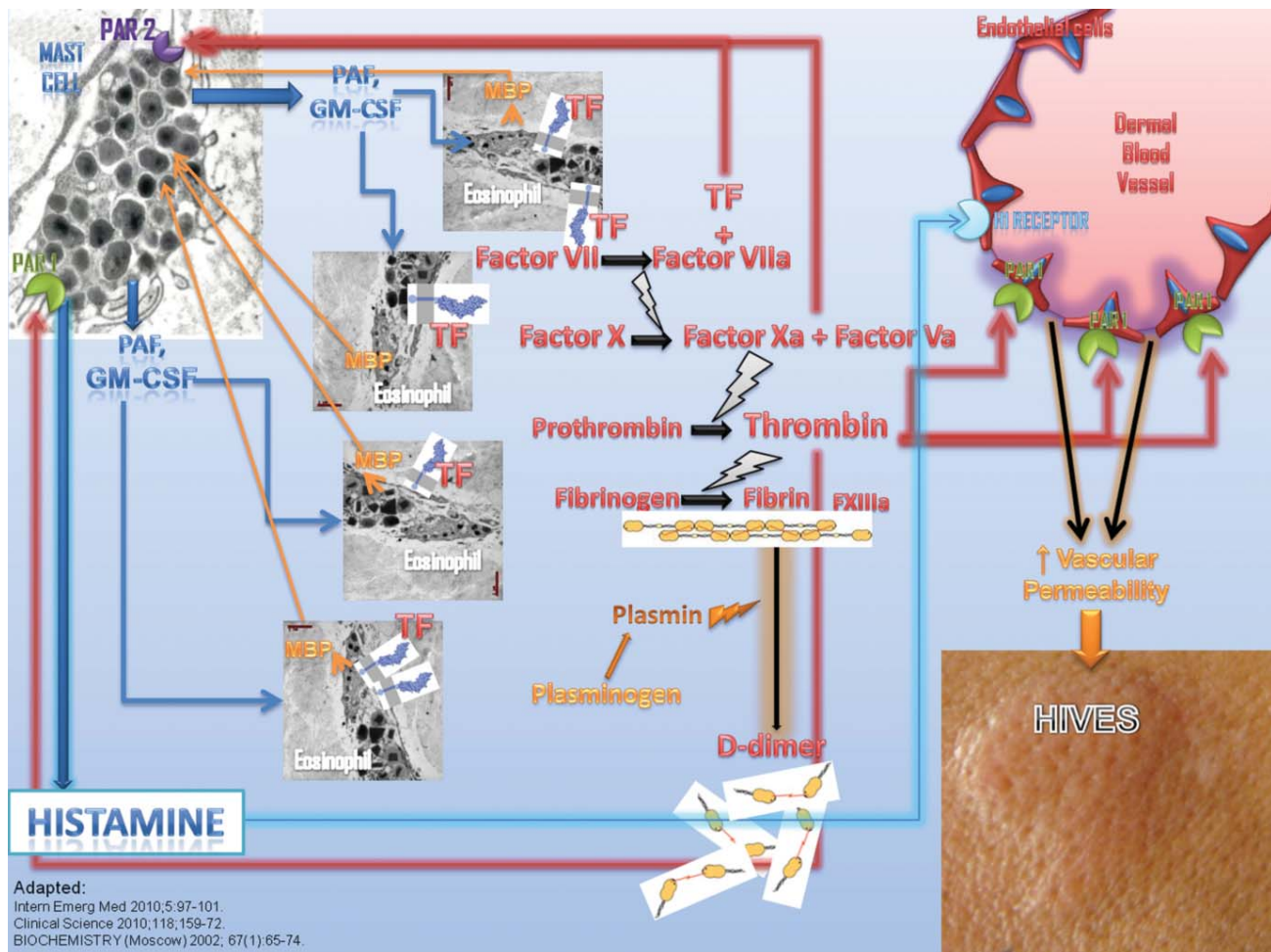
N= number of patients OR= odds ratio.



GRAPH 1: Average concentrations of D-dimer (ng/ml FEU): gender and diseases

TABLE 3: Demographic data and frequency of elevated D-dimer levels among patients with urticarial vasculitis

Patient #	Age	Gender	Urticarial Vasculitis under activity	Normocomplementemic Urticarial Vasculitis (NUV) or Hypocomplementemic Urticarial Vasculitis (HUV)	D-dimer levels (ng/ml FEU)
1	29	Female	Yes	HUV	2.600
2	59	Male	Yes	NUV	890
3	38	Female	Yes	HUV	780
4	48	Female	Yes	NUV	1.200
5	39	Female	Yes	NUV	900



**FIGURE 1:** Proposition of events involving the coagulation cascade in chronic urticaria: During activation of mast cells occurs the release of vasoactive amines (mainly histamine), eicosanoids, and cytokines. Histamine H1 receptors act on endothelial cells promoting vasodilatation and increasing capillary permeability. GM-CSF (Granulocyte/macrophage colony-stimulating factor) and PAF (platelet activating factor) are able to activate eosinophils in the dermis and promote the expression of tissue factor (TF) in their cytoplasm membrane. Activated eosinophils secrete major basic protein (MBP) that stimulates mast cells. Besides these events, TF generated by eosinophils may start the extrinsic pathway of coagulation forming the complex VIIa+TF, that together with complex Xa+Va, act in mast cells via protease activated receptor 2 (PAR2). Thrombin activates: (i) PAR 1 on endothelial cells leading to the secretion and expression of the mediators of inflammation and anticoagulants (ICAM-1, NO and others); (ii) PAR1 of mast cells inducing the secretion of pro-inflammatory (histamine, PAF, cytokines, and others) and anti-inflammatory (heparin, NO) mediators. The fibrin is then degraded by fibrinolytic system in fibrin degradation products (FDP), including d-dimer, which can be detected in peripheral blood. Abbreviations: PAR, protease activated receptor; ICAM, intercellular adhesion molecule; NO, nitric oxide

The exposure of subendothelial TF to blood after vessel injury is a critical step in hemostasis and in the pathogenesis of arterial and venous thrombotic disorders. Moreover, there is an additional role for overexpression of TF and subsequent generation of TF: FVIIa complex, FXa and thrombin have recently emerged as contributors in non-thrombotic manifestations such as inflammation, cancer growth and fibrosis.<sup>17</sup>

Urticarial vasculitis usually presents with a considerable number of intact and degenerated neu-

trophils, resulting in “nuclear dust”, which together with edema of the dermis and fibrinoid necrosis of small diameter blood vessels of the superficial dermis compose the typical histopathology pattern of this disease.<sup>18</sup> Recently some authors showed that the activated fraction of C5 complement, when bound to its receptor on the membrane of neutrophils, activate these cells and begin to express tissue factor in their cytoplasm membranes. Moreover, C5a can induce thrombosis by increasing TF expression on endothelial cells and monocytes in mice.<sup>19,20</sup> Ritis et al. report-

ed the same results in humans.<sup>21</sup> The expression of tissue factor may activate the extrinsic pathway of coagulation, generating thrombin and fibrin, which, under fibrinolysis may produce D-dimer. Thus, this sequence of events may explain our findings of elevated d-dimer in plasma of patients with urticarial vasculitis during disease activity.

## CONCLUSIONS

Patients with active chronic urticaria have higher serum levels of D-dimer when compared to patients with chronic urticaria under remission.

Patients with chronic urticaria under remission and patients with psoriasis, presented with normal serum levels of D-dimer.

Patients with urticarial vasculitis presented with elevated serum D-dimer levels, an indirect evidence of activation of blood coagulation cascade. □

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