



Activation of the Intrinsic Coagulation Pathway in Patients With Chronic Urticaria

Jung-Ah Kim,¹ Sujeoung Kim,^{2,3} Ji-Eun Kim,^{1,4} Ja-Yoon Gu,^{1,4} Hyun Ju Yoo,^{1,4} Hye-Ryun Kang,^{2*} Hyun Kyung Kim^{1,4*}

¹Department of Laboratory Medicine, ²Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

³Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, Korea

⁴Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

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Purpose: Although coagulation activation has been reported in chronic urticaria, data pertaining to detailed changes in coagulation factors and global coagulation status are lacking. The current study evaluated global coagulation status in patients with chronic urticaria using thrombin generation assay (TGA) and the levels of individual coagulation factors. **Methods:** Patients with chronic urticaria (n=57) and 20 healthy controls were enrolled. TGA was performed under stimulation with 2 concentrations of tissue factor (TF). Coagulation factors and conventional coagulation assays were also analyzed. **Results:** Although patients with chronic urticaria showed prolonged activated partial thromboplastin time, prothrombin time did not differ significantly between patients and controls. In both 1 pM and 5 pM TF-stimulated TGA, peak thrombin and endogenous thrombin potential (ETP) levels were markedly decreased in patients with chronic urticaria. As expected, intrinsic coagulation factors (VIII, IX, and XII), as well as coagulation factors of the common pathway (II, V, and X), were consistently decreased. Additionally, D-dimer was significantly increased in patients as compared to controls. In multivariate regression analysis, the presence of chronic urticaria was the only significant independent contributor to the low ETP value. **Conclusions:** Chronic urticaria is characterized by *in vivo* coagulation activation through the intrinsic coagulation pathway, which can be measured with sensitivity using TGA.

Key Words: Chronic urticaria; coagulation factors; contact pathway; intrinsic coagulation pathway; thrombin generation assay

INTRODUCTION

Chronic urticaria is defined as recurrent eruptions of short-lived swellings due to plasma leakage from small blood vessels into the surrounding connective tissue.¹ Several factors are considered causes of the disease, including food allergies, emotional disturbances, intolerance to food additives, and chronic infections.^{2,3} Autoimmunity is also considered an integral part of the pathophysiology of chronic urticaria, as injections of autologous serum have caused wheal and flare reactions, and several autoantibodies, such as anti-IgE and anti-FcεRI, have been identified in patients with chronic urticaria.⁴⁻⁶ However, these antibodies are only detectable in one-third of chronic urticaria cases, and the autologous serum skin test (ASST) has failed to elicit a wheal-flare reaction in approximately half of chronic urticaria cases.^{5,6} Therefore, other factors may be involved in the pathogenesis of chronic urticaria.

Recently, activation of the coagulation pathway, including increased thrombin-antithrombin and D-dimer, has been demonstrated in chronic urticaria.^{2,7-9} The coagulation pathway is

closely associated with the inflammation system. More specifically, inflammation activates coagulation, and coagulation provokes the inflammatory system.¹⁰ Tissue factor (TF) has been considered an initiator of coagulation activation.¹¹ For example, the expression of TF in skin specimens from patients with urticaria was considered evidence of coagulation activation in urticarial tissue.¹² On the other hand, a contact system that can trigger coagulation activation has been shown to contribute to in-

Correspondence to: Hye-Ryun Kang, MD, PhD, Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea.
Tel: +82-2-2072-0820, Fax: +82-2-764-2199, E-mail: helenmed@snu.ac.kr

Hyun Kyung Kim, MD, PhD, Department of Laboratory Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea.
Tel: +82-2-2072-0853, Fax: +82-2-747-0359, E-mail: lukekhk@snu.ac.kr
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- Jung-Ah Kim and Sujeoung Kim contributed equally to this paper.
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flammatory or coagulation processes *in vivo*.¹³ There are diverse and widely used clinical laboratory tests for the routine screening and evaluation of the coagulation system, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time. However, these assays may fail to detect blood coagulation abnormalities.¹⁴ In recent years, a global coagulation assay known as the thrombin generation assay (TGA) has been developed in order to measure coagulation disturbances with greater sensitivity. In the TGA, addition of TF into the test plasma induces dynamical thrombin generation in the plasma, which can then be measured as the endogenous thrombin potential (ETP). The ETP represents combined coagulation effects from all of the coagulation and anticoagulation factors that exist in the plasma.¹⁵ Because thrombin is an essential product of coagulation amplification, a low ETP level represents hemorrhagic tendencies or *in vivo* consumption of coagulation factors, while high ETP levels represent thrombotic tendencies.^{16,17}

To elucidate a detailed process of coagulation disturbance in chronic urticaria, it is necessary to assess blood coagulation potential with a keen coagulation test. This study evaluated global coagulation status in patients with chronic urticaria using TGA as well as conventional global assays, such as PT and aPTT. In addition, to clarify the causative contributor(s) of the coagulation disturbance, all coagulation factors were measured.

MATERIALS AND METHODS

Study population

This study was reviewed and approved by the Institutional Review Board of Seoul National University College of Medicine, and all subjects provided signed informed consent. Adult patients diagnosed as having chronic urticaria at the Allergy Department of the Seoul National University Hospital (n=57) were enrolled. Urticaria that persisted for longer than 6 weeks was defined as chronic. We excluded patients who had received anticoagulants or steroids within 7 days of study initiation. Of the total patient population, 38.6% were men and 61.4% were women, and their median age was 40.1 years. Of the 44 patients who underwent ASST as previously described,⁷ 16 (36%) showed positive results. Some of the patients with chronic urticaria exhibited comorbidities, including asthma (n=3), allergic rhinitis (n=7), thyroid cancer (n=1), hyperthyroidism (n=1), hypothyroidism (n=3), systemic lupus erythematosus (n=1), and Sjögren's syndrome (n=1). In addition, 20 healthy controls with a median age of 45.0 years were included.

Specimen collection

Peripheral blood samples were collected in commercial tubes containing 0.109 M sodium citrate (Becton Dickinson, San Jose, CA, USA). Within 1 hour after blood collection, plasma was separated by centrifugation of whole blood at 1,550 g for 15

minutes. The aliquots of plasma were stored at -80°C and used for the coagulation tests within 6 months.

Coagulation assays

PT and aPTT were measured using HemosIL RecombiPlasTin and SynthASil reagents (Instrumentation Laboratory SpA, Milan, Italy), respectively. Fibrinogen was measured using the HemosIL Fibrinogen-C XL reagent (Instrumentation Laboratory SpA). Coagulation factors were assayed using a PT-based clotting assay (for FII, FV, FVII, and FX) with the HemosIL RecombiPlasTin reagent, and an aPTT-based clotting assay (for FVIII, FXI, FXI, and FXII) with the SynthASil reagent. Antithrombin activity was determined by chromogenic assays (HemosIL liquid Antithrombin; Instrumentation Laboratory SpA). These coagulation tests were performed using an ACL 3000 automated coagulation analyzer (Beckman Coulter, Fullerton, CA, USA). The reference ranges of PT and aPTT were 9.5-12.5 seconds and 26.7-36.6 seconds, respectively.

Thrombin generation assay

TF-triggered thrombin generation in platelet-poor plasma was measured using the calibrated automated thrombogram method (Thrombinoscope BV, Maastricht, The Netherlands) as previously described.¹⁸ Briefly, 20 µL of reagent containing TF at a final concentration of 1 pM or 5 pM (PPP Reagent 5 pM or PPP Reagent Low, respectively; Thrombinoscope BV), along with phospholipids or thrombin calibrators, were dispensed into each well of round-bottomed 96-well plates, prior to the addition of 80 µL of test plasma. After the addition of 20 µL of fluorogenic substrate in HEPES buffer containing CaCl₂, the fluorescent signal was read in a Fluoroskan Ascent fluorometer (Thermo Labsystems OY, Helsinki, Finland), and thrombin generation curves were calculated using Thrombinoscope software (Thrombinoscope BV). Thrombin generation curves were evaluated using parameters that described initiation, propagation, and termination phases of thrombin generation, namely, lag time, ETP, and peak thrombin height (peak thrombin). The lag time, defined as the time to reach one-sixth of the peak height, is considered a measure of the initiation phase and is equivalent to the clotting time. The peak height was defined as the maximum thrombin concentration produced. ETP, the area under the thrombin generation curve, represented the total amount of the thrombin generated.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics version 21 (IBM Corporation, Armonk, NY, USA). Continuous data comparisons were performed using the Mann-Whitney *U* and Kruskal-Wallis tests, and the relationships between categorical variables were compared using the chi-square test. The optimal cutoff value was determined with a receiver operating characteristic (ROC) analysis using MedCalc (MedCalc

Software, Mariakerke, Belgium). Multivariate logistic regression analysis was conducted in order to estimate the prediction power of urticarial coagulation disturbance. Multiple linear regression was also performed to investigate the influence of clinical and laboratory parameters on ETP values. Two-sided *P* values <0.05 were considered statistically significant.

RESULTS

Conventional laboratory profiles in patients with chronic urticaria

The clinical and laboratory characteristics of the healthy controls and patients with urticaria are shown in Table 1. Although the mean age of the controls was slightly older than that of the patients, there was no difference in gender between the groups. Compared to the controls, patients with urticaria showed significantly higher white blood cell counts. However, there was no difference in hemoglobin or platelet counts between the groups.

Among conventional coagulation tests, the PT of patients was similar to that of controls. Interestingly, the aPTT was slightly prolonged in the patients as compared to the controls. The fibrinogen level was similar between the groups.

Global coagulation status in patients with chronic urticaria

In 1 pM TF-stimulated TGA, peak thrombin and ETP levels were markedly decreased in patients with chronic urticaria (Table 2). However, there were no significant differences in lag time or time-to-peak between controls and patients. Similarly, peak thrombin and ETP were significantly lower in patients than in controls in 5 pM TF-stimulated TGA. The lag time and

time-to-peak were correspondingly prolonged in patients as compared to controls.

To investigate detailed causes of the observed hemostatic disturbances, plasma levels of all coagulation factors were measured (Table 2). As expected, intrinsic coagulation factors (VIII, IX, and XII), as well as coagulation factors of the common pathway (II, V, and X), were consistently decreased in patients as compared to controls. Factor XI was also slightly decreased in patients as compared to controls, although this difference did not reach the level of statistical significance. Conversely, D-dimer was significantly increased in the patients as compared to the controls. According to smoking history, there were no significant differences in coagulation results (data not shown). When assessed only in patients, there were no differences according to ASST positivity (data not shown).

Prediction power of global coagulation tests with regard to coagulation disturbances in chronic urticaria

To compare the prediction power of global coagulation tests with regard to coagulation disturbances in chronic urticaria, age- and sex-adjusted logistic regression analyses were performed (Table 3). We divided the study population into 2 groups according to global coagulation test values by using the best cutoff value determined from the ROC analysis. PT did not show any prediction power. However, the aPTT showed a significant power to predict coagulation disturbances in chronic urticaria. In 1 pM TF-stimulated TGA, ETP showed a high odds ratio for predicting coagulation disturbances in chronic urticaria. Notably, the odds ratio of peak thrombin in 5 pM TF-stimulated TGA was the highest among the TGA parameters.

To determine the contributing value of clinical and laboratory

Table 1. Clinical and laboratory findings from healthy controls and patients with urticaria

	Healthy controls (n=20)	Patients with urticaria (n=57)	* <i>P</i> -value
Age (year)	45.0 ± 6.2	40.1 ± 14.5	0.044
Male/Female (n)	10 (50%)/10 (50%)	22 (38.6%)/35 (61.4%)	0.434
Hemoglobin (g/dL)	14.7 (13.1–15.7)	14.0 (12.8–15.4)	0.670
WBC (× 10 ⁹ /L)	5.05 (4.33–5.98)	6.61 (5.44–7.98)	<0.001
Segmented neutrophil	2.89 (2.47–3.42)	3.77 (3.11–4.56)	<0.001
Lymphocyte	1.80 (1.54–2.13)	2.35 (1.94–2.84)	<0.001
Monocyte	0.27 (0.23–0.32)	0.35 (0.29–0.42)	<0.001
Eosinophil	0.10 (0.08–0.11)	0.13 (0.10–0.15)	<0.001
Basophil	0.03 (0.01–0.04)	0.02 (0.01–0.03)	0.025
Platelet (× 10 ⁹ /L)	238.5 (210.0–271.8)	260.0 (219.0–293.0)	0.163
PT (s)	11.5 (11.1–12.1)	11.4 (10.7–11.9)	0.407
aPTT (s)	32.0 (31.0–33.0)	34.9 (32.2–36.6)	<0.001
Fibrinogen (%)	281.3 (253.2–313.1)	298.3 (255.9–335.8)	0.332

*The Mann–Whitney *U* and χ^2 -tests were used for continuous and categorical variables, respectively.

Data are shown as the median (interquartile range) for continuous variables or as number (percentage) for categorical variables, with the exception of age, which is presented as the mean ± standard deviation.

WBC, white blood cell count; PT, prothrombin time; aPTT, activated partial thromboplastin time.

Table 2. Coagulation profiles of healthy controls and urticarial patients

	Healthy controls (n=20)	Urticarial patients (n=57)	*P-value
TGA (1 pM TF)			
Peak thrombin (nM)	191.6 (142.2–216.8)	73.8 (44.5–127.7)	<0.001
ETP (nM/min)	1,278.0 (1092.5–1418.8)	653.0 (448.3–962.0)	<0.001
Lag time (min)	9.3 (8.1–10.3)	9.5 (8.1–12.3)	0.307
Time-to-peak (min)	13.0 (11.7–14.0)	13.8 (11.4–16.6)	0.220
TGA (5 pM TF)			
Peak thrombin (nM)	258.5 (230.8–289.5)	91.0 (63.7–119.6)	<0.001
ETP (nM/min)	1,760.0 (1420.8–1760.0)	702.9 (612.9–1064.5)	<0.001
Lag time (min)	4.0 (3.5–4.7)	5.00 (4.0–5.9)	0.006
Time-to-peak (min)	7.0 (6.3–8.2)	9.5 (7.6–11.5)	<0.001
Factor II (%)	104.4 (98.9–113.6)	98.0 (89.6–107.2)	0.021
Factor V (%)	91.2 (81.9–98.0)	77.4 (64.2–94.5)	0.008
Factor VII (%)	103.6 (95.8–120.3)	106.2 (90.9–134.6)	0.741
Factor VIII (%)	105.6 (91.7–121.6)	92.5 (67.0–112.5)	0.027
Factor IX (%)	112.2 (102.8–126.8)	101.2 (87.5–112.6)	0.015
Factor X (%)	113.0 (100.1–121.3)	102.6 (96.5–114.0)	0.043
Factor XI (%)	102.3 (96.6–126.0)	98.6 (87.9–105.8)	0.142
Factor XII (%)	71.6 (62.4–98.5)	58.2 (54.0–93.0)	0.012
Antithrombin (%)	107.5 (101.0–113.0)	99.6 (90.1–112.6)	0.087
D-dimer (µg/mL)	50.0 (39.4–83.8)	246.7 (130.3–437.3)	<0.001

*The Mann–Whitney *U* test was used for continuous variables.

Data are shown as the median (interquartile range) for continuous variables.

TGA, thrombin generation assay; TF, tissue factor; ETP, endogenous thrombin potential.

Table 3. Prediction power of urticarial coagulation disturbance in global coagulation tests

	Healthy controls (n=20)	Urticarial patients (n=57)	Logistic regression analysis		
			OR	95% CI	P-value
PT (> 10.7 s)	19/20 (95%)	42/57 (73.7%)	0.13	0.02–1.09	0.060
aPTT (> 34 s)	1/20 (5%)	34/57 (59.6%)	29.84	3.61–246.35	0.002
TGA (1 pM TF)					
Peak thrombin (≤ 130.0 nM)	3/20 (15%)	44/57 (77.2%)	17.67	4.40–70.97	<0.001
ETP (≤ 983 nM/min)	1/20 (5%)	45/57 (78.9%)	84.45	8.99–793.33	<0.001
Lag time (> 10.33 min)	4/20 (20%)	27/57 (47.4%)	5.38	1.42–20.36	0.013
Time-to-peak (> 14 min)	3/20 (15%)	28/57 (49.1%)	6.79	1.67–27.60	0.007
TGA (5 pM TF)					
Peak thrombin (≤ 189.9 nM)	1/20 (5%)	54/57 (94.7%)	1396.90	39.16–49,830.27	<0.001
ETP (≤ 1,164.00 nM/min)	1/20 (5%)	47/57 (82.5%)	89.48	10.37–772.44	<0.001
Lag time (> 5.32 min)	2/20 (0%)	22/57 (38.6%)	5.48	1.15–26.20	0.033
Time-to-peak (> 8.3 min)	2/20 (10%)	37/57 (64.9%)	17.36	3.53–85.27	<0.001

The parameter cutoff values were determined as the values at which the best thrombotic predictive value was produced. The odds ratios were adjusted for age and sex.

OR, odds ratio; CI, confidence interval; PT, prothrombin time; aPTT, activated partial thromboplastin time; TGA, thrombin generation assay; TF, tissue factor; ETP, endogenous thrombin potential.

parameters to ETP, we performed linear regression analyses in the total population (Table 4). In univariate regression analysis, the presence of urticaria strongly decreased the ETP levels observed in 1 pM TF-stimulated TGA. The aPTT value was also

found to be a significant contributing factor to the ETP levels observed in 1 pM TF-stimulated TGA. In a multivariate regression analysis, the presence of urticaria was the only significant independent contributor to the ETP levels observed in 1 pM

Table 4. Contributions of clinical and laboratory parameters to the endogenous thrombin potential in the total population (n = 77)

Response variables	Explanatory variables	Univariable regression			Multivariable regression		
		β	SE	P	β	SE	P
ETP (1 pM TF)	Age	3.874	3.833	0.315	0.495	3.171	0.876
	Female sex	-102.532	100.342	0.310	4.119	81.012	0.960
	Urticaria	-576.675	91.985	<0.001	-533.612	105.242	<0.001
	WBC	-50.866	25.536	0.050	8.460	22.884	0.713
	PT	-34.797	22.149	0.120	-12.989	20.990	0.538
	aPTT	-47.758	12.890	<0.001	-21.421	13.909	0.128
ETP (5 pM TF)	Age	5.926	3.916	0.134	1.052	2.730	0.701
	Female sex	-114.177	103.235	0.272	-3.104	69.752	0.965
	Urticaria	-748.126	78.861	<0.001	-723.735	90.614	<0.001
	WBC	-64.181	26.166	0.017	11.783	19.703	0.552
	PT	-13.005	23.138	0.576	6.676	18.073	0.713
	aPTT	-47.207	13.373	0.001	-17.272	11.975	0.154

β represents regression coefficients.

SE, standard error; ETP, endogenous thrombin potential; WBC, white blood cell count; PT, prothrombin time; aPTT, activated partial thromboplastin time.

TF-stimulated TGA. Similar results were also found in the analysis of contributing factor(s) to the ETP levels observed in 5 pM TF-stimulated TGA.

DISCUSSION

Results from the current study demonstrated a coagulation disturbance in patients with chronic urticaria. Although these patients showed prolonged aPTT, differences in PT were not detected between patients and controls. This prolonged aPTT was found to be attributable to deficiencies of intrinsic coagulation factors. TGAs detected the coagulation disturbance associated with chronic urticaria with greater sensitivity than conventional coagulation tests, such as aPTT. Additionally, chronic urticaria was revealed to be an independent contributing factor to the ETP value.

The coagulation cascade has been implicated in the pathogenesis of urticaria.^{2,7-9} More specifically, study results have revealed elevated plasma markers of thrombin generation, such as factor VIIa, thrombin-antithrombin complex, and D-dimer.⁹ However, detailed changes in individual coagulation factors have yet to be elucidated. For the first time in chronic urticaria, the current study investigated plasma levels of individual coagulation factors and revealed selective deficiencies of coagulation factors involved in the intrinsic pathway.

In general, the *in vivo* coagulation process occurs through the extrinsic pathway and is initiated by the binding of factor VII to TF.¹⁹ Although factor XII can also act as an initiator of the intrinsic coagulation pathway, it is not thought to mediate the *in vivo* coagulation process because factor XII deficiency was not associated with bleeding.²⁰ The contact system consists of factor XII, factor XI, prekallikrein, and high-molecular-weight kininogen.

Activation of the contact system can initiate the coagulation cascade through factor XII activation. For example, activation of the contact system is a frequent occurrence in angioedema.²¹ To date, little is known regarding contact factor activation in urticaria; however, it is plausible that the contact factor activation observed in patients with urticaria in the current study was attributable to the selective deficiency of intrinsic coagulation factors, including contact coagulation factor XII, that they exhibited.

The extrinsic pathway is not likely to be involved in the coagulation activation of urticaria because factor VII levels were not decreased in patients with chronic urticaria in the current study. However, reports of TF expression in skin specimens from patients with urticaria^{12,22} may provide indirect evidence for extrinsic coagulation activation. Furthermore, the results of a previous study demonstrated that activated factor VII levels were higher in the acute state of urticaria, but not significantly different in chronic urticaria,²³ suggesting that extrinsic coagulation activation may occur in acute urticaria.

Results from the current study also demonstrated high D-dimer levels in patients with urticaria. D-dimer is a sensitive marker of fibrin deposits formed through *in vivo* activation of the coagulation process. It also provides indirect evidence of thrombin generation, which activates mast cell degranulation, and induces vascular permeability.^{24,25} Therefore, active thrombin generation may aggravate the urticarial process and provide a rationale for anticoagulant treatment.

The results of the current study provide further evidence of the utility of laboratory tests that measure thrombin generation in patients with chronic urticaria. TGA is a sensitive assay used to measure global hemostatic potential in peripheral blood.²⁶ Because the extent of *in vivo* coagulation activation is deter-

mined through combined effects of coagulation and anticoagulation factors, a global coagulation test is more valuable to assess *in vivo* coagulation activation than measurements of individual coagulation factors. As expected, the ETP and peak thrombin results obtained from TGA sensitively detected the coagulation activation status of patients with chronic urticaria in the current study. Because coagulation activation induces mild consumption of coagulation factors, the amount of residual thrombin generation was low, as exhibited by low levels of ETP and peak thrombin. Correspondingly, the lag time and time-to-peak were prolonged due to decreased coagulation factors, which required more time to form thrombin *in vitro*. Likewise, the current study demonstrated the influence of urticaria on ETP levels in a linear regression analysis. The presence of urticaria contributed to ETP more strongly than other conventional coagulation parameters, such as PT and aPTT (Table 4).

The current study has several limitations. First, we could not investigate coagulation profiles with regard to disease severity and course. Second, an appropriate biomarker of contact activation remains to be explored in future studies in order to clarify the cause(s) of the observed intrinsic factor deficiencies. Third, the median age of the healthy controls was slightly higher than that of the patients. However, we speculated that the age difference did not influence our results because: (1) the age difference was slight, and (2) the logistic regression analysis was adjusted for age. Last but not least, the clinical meaning of subtle prolongation of aPTT in the urticarial patients was not clarified in this study. Therefore, prospective studies to intervene coagulation activity is needed to evaluate the pathophysiologic role of intrinsic factor deficiencies in chronic urticaria.

In summary, patients with chronic urticaria showed a prolonged aPTT compared to healthy controls. The PT value of patients did not differ from that of healthy controls. We also demonstrated that the intrinsic coagulation factors were mainly decreased in urticaria, suggesting a possible association with contact factor activation. Global coagulation status, as assessed through TGA, keenly demonstrated the *in vivo* coagulation activation of urticaria by showing more prominent changes in test parameters than those associated with conventional PT and aPTT. In conclusion, chronic urticaria is characterized by *in vivo* coagulation activation through the intrinsic coagulation pathway, which can be sensitively measured using TGA.

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ORCID

Jung-Ah Kim <http://orcid.org/0000-0001-6934-1987>

REFERENCES

- Cugno M, Asero R, Tedeschi A, Lazzari R, Marzano AV. Inflammation and coagulation in urticaria and angioedema. *Curr Vasc Pharmacol* 2012;10:653-8.
- 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.
- Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Gimenez-Arnau AM, et al. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009;64:1427-43.
- Greaves M. Chronic urticaria. *J Allergy Clin Immunol* 2000;105:664-72.
- Grattan CE, Wallington TB, Warin RP, Kennedy CT, Bradfield JW. A serological mediator in chronic idiopathic urticaria--a clinical, immunological and histological evaluation. *Br J Dermatol* 1986;114:583-90.
- Gruber BL, Baeza ML, Marchese MJ, Agnello V, Kaplan AP. Prevalence and functional role of anti-IgE autoantibodies in urticarial syndromes. *J Invest Dermatol* 1988;90:213-7.
- 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;117:1113-7.
- Asero R, Tedeschi A, Riboldi P, Griffini S, Bonanni E, Cugno M. Severe chronic urticaria is associated with elevated plasma levels of D-dimer. *Allergy* 2008;63:176-80.
- Wang F, Tang H, Xu JH, Kang KF. Activation of the blood coagulation cascade is involved in patients with chronic urticaria. *J Allergy Clin Immunol* 2009;123:972-3.
- Petaja J. Inflammation and coagulation. An overview. *Thromb Res* 2011;127 Suppl 2:S34-7.
- van der Poll T. Tissue factor as an initiator of coagulation and inflammation in the lung. *Crit Care* 2008;12 Suppl 6:S3.
- Cugno M, Marzano AV, Tedeschi A, Fanoni D, Venegoni L, Asero R. Expression of tissue factor by eosinophils in patients with chronic urticaria. *Int Arch Allergy Immunol* 2009;148:170-4.
- de Maat S, Tersteeg C, Herczenik E, Maas C. Tracking down contact activation--from coagulation *in vitro* to inflammation *in vivo*. *Int J Lab Hematol* 2014;36:374-81.
- Kitchens CS. To bleed or not to bleed? Is that the question for the PTT? *J Thromb Haemost* 2005;3:2607-11.
- Kim SY, Kim JE, Kim HK, Kim I, Yoon SS, Park S. Influence of coagulation and anticoagulant factors on global coagulation assays in healthy adults. *Am J Clin Pathol* 2013;139:370-9.
- Hron G, Kollars M, Binder BR, Eichinger S, Kyrle PA. Identification of patients at low risk for recurrent venous thromboembolism by measuring thrombin generation. *JAMA* 2006;296:397-402.
- Jeong JC, Kim JE, Ryu JW, Joo KW, Kim HK. Plasma haemostatic potential of haemodialysis patients assessed by thrombin generation assay: hypercoagulability in patients with vascular access thrombosis. *Thromb Res* 2013;132:604-9.
- Seo JW, Kim HK, Kim JE, Park S, Cho HI. Prognostic values of the factor Xa-activated clotting time and endogenous thrombin potential in patients suspected of having disseminated intravascular coagulation. *Thromb Res* 2009;123:565-72.
- Sere KM, Hackeng TM. Basic mechanisms of hemostasis. *Semin Vasc Med* 2003;3:3-12.

20. Bennett B, Ratnoff OD, Holt JB, Roberts HR. Hageman trait (factor XII deficiency): a probably second genotype inherited as an autosomal dominant characteristic. *Blood* 1972;40:412-5.
21. Hentges F, Hilger C, Kohnen M, Gilson G. Angioedema and estrogen-dependent angioedema with activation of the contact system. *J Allergy Clin Immunol* 2009;123:262-4.
22. Asero R, Tedeschi A, Coppola R, Griffini S, Paparella P, Riboldi P, et al. Activation of the tissue factor pathway of blood coagulation in patients with chronic urticaria. *J Allergy Clin Immunol* 2007;119:705-10.
23. Zhu H, Liang B, Li R, Li J, Lin L, Ma S, et al. Activation of coagulation, anti-coagulation, fibrinolysis and the complement system in patients with urticaria. *Asian Pac J Allergy Immunol* 2013;31:43-50.
24. Schaeffer RC Jr, Gong F, Bitrick MS Jr, Smith TL. Thrombin and bradykinin initiate discrete endothelial solute permeability mechanisms. *Am J Physiol* 1993;264:H1798-809.
25. Vliagoftis H. Thrombin induces mast cell adhesion to fibronectin: evidence for involvement of protease-activated receptor-1. *J Immunol* 2002;169:4551-8.
26. Lee K, Kim JE, Kwon J, Kim I, Yoon SS, Park S, et al. Poor prognosis of hypocoagulability assessed by thrombin generation assay in disseminated intravascular coagulation. *Blood Coagul Fibrinolysis* 2014;25:241-7.