

Elevated plasma von Willebrand factor levels in patients with active ulcerative colitis reflect endothelial perturbation due to systemic inflammation

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Abstract

AIM: To evaluate the plasma von Willebrand factor (vWF) levels in patients with ulcerative colitis (UC) and to investigate their relationship with disease activity, systemic inflammation and coagulation activation.

METHODS: In 46 patients with ulcerative colitis (active in 34 patients), clinical data were gathered and plasma vWF levels, markers of inflammation (ESR, CRP, and fibrinogen) and thrombin generation (TAT, F1+2, and D-dimers) were measured at baseline and after 12 wk of treatment. Plasma vWF levels were also determined in 52 healthy controls (HC). The relationship of plasma vWF levels with disease activity, disease extent, response to therapy, acute-phase reactants (APRs) and coagulation markers (COAGs) was assessed.

RESULTS: The mean plasma vWF concentrations were significantly higher in active UC patients (143.38 ± 63.73%) than in HC (100.75 ± 29.65%, $P = 0.001$) and inactive UC patients (98.92 ± 43.6%, $P = 0.031$). ESR, CRP and fibrinogen mean levels were significantly higher in active UC patients than in inactive UC patients, whereas there were no significant differences in plasma levels of D-dimers, F1+2, and TAT. UC patients with raised APRs had significantly higher mean plasma vWF levels than those with normal APRs (144.3% vs 96.2%, $P = 0.019$), regardless of disease activity. Although the mean plasma vWF levels were higher in UC patients with raised COAGs than in those with normal COAGs, irrespective of disease activity, the difference was

not significant (141.3% vs 118.2%, $P = 0.216$). No correlation was noted between plasma vWF levels and disease extent. After 12 wk of treatment, significant decreases of fibrinogen, ESR, F1+2, D-dimers and vWF levels were noted only in UC patients with clinical and endoscopic improvement.

CONCLUSION: Our data indicate that increased plasma vWF levels correlate with active ulcerative colitis and increased acute-phase proteins. Elevated plasma vWF levels in ulcerative colitis possibly reflect an acute-phase response of the perturbed endothelium due to inflammation. In UC patients, plasma vWF levels may be another useful marker of disease activity or response to therapy.

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INTRODUCTION

The etiology and pathogenesis of inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD), are still unclear^[1]. "Vascular" theory supports that intestinal vascular injury is involved in CD and UC pathogenesis^[2,3].

There is evidence that a hypercoagulable state exists in IBD, which might play a role in IBD pathogenesis^[3-5]. This theory is further supported by the observation of Gaffney *et al*^[6], that patients with hemophilia and von Willebrand's disease have a lower risk in developing IBD and by the beneficial effects of heparin in the treatment of refractory ulcerative colitis^[7,8]. The hypercoagulable state has been found to exist both in active and in inactive disease^[9-15]. Furthermore, endothelial dysfunction, due to effects of

increased proinflammatory cytokines (IL-1, TNF- α), seems to play a central role in the hypercoagulant state production in IBD and also provides an evidence of interrelation between coagulation and inflammation pathways^[16-18].

von Willebrand factor (vWF) is a large glycoprotein which circulates in human plasma or is deposited into the vascular subendothelium. Approximately 85% of circulating vWF is synthesized by the vascular endothelial cells, which are the main source of synthesis and secretion of this coagulation factor. vWF is also synthesized by megakaryocytes and is contained in platelets, which derive the remaining 15% of the circulating protein in blood. vWF serves as a stabilizing carrier protein of the coagulation factor VIII in circulation. vWF also mediates platelet to platelet interactions and platelet adhesion to the subendothelium in response to endothelial injury during the first step of thrombus formation^[19]. Increased circulating levels of vWF in serum are considered as a marker of endothelial dysfunction or injury^[19,20]. Increased levels of vWF are also observed as an acute-phase response in various inflammatory conditions^[21].

vWF serum levels have been reported to be increased in patients with IBD, but it is not clear whether they reflect primary endothelial damage^[17,22-25] or they are a manifestation of acute-phase response due to inflammation^[22,23,26].

In this study, in order to clarify the meaning of elevated vWF levels in ulcerative colitis, we measured the circulating plasma vWF levels in a group of patients with ulcerative colitis and investigated their relationship with clinical activity and endoscopic severity of disease, markers of systemic inflammation and thrombin generation. We also monitored the changes of these variables during 12 wk of therapy and estimated their relationship with the clinical outcome.

MATERIALS AND METHODS

Patients and controls

Forty-six patients with ulcerative colitis (30 males and 16 females, mean age 41.8 years, range 17-73 years) and 52 healthy individuals (healthy controls, HC) (30 males and 22 females, mean age 40.9 years, range 19-65 years) were consecutively included in the study. All patients and controls were from the same geographical area (Northern Greece) and had a Greek ancestry.

Methods

The diagnosis of UC was based on the standard clinical, endoscopic and histological criteria. A complete medical history was obtained and physical examination was performed in all UC patients. **During baseline evaluation**, disease activity in patients with UC (active or inactive) was assessed with the simple clinical colitis activity index (SCCAI), **taking into account five clinical criteria: day and night stool frequency, urgency of defecation, blood in the stool, general well being and presence of extracolonic manifestations**^[27]. A SCCAI score of ≤ 2 points was defined as clinical remission. Baseline colonoscopy with biopsy sampling was performed in all patients with UC, in order to assess the endoscopic severity and extent of dis-

ease. Endoscopic severity was measured by a modified endoscopic score with an 18-point scale^[28] involving nine parameters: erythema, vascular pattern, friability, granularity, spontaneous bleeding, occurrence and severity of ulcers, extent of ulcerated surface, and presence of mucopurulent exudates. All parameters were scored from 0 to 2 points. Four grades of activity were considered according to the sum of all parameters: inactive disease (0-3), mild disease (4-7), moderate disease (8-12), and severe disease (13-18). Grading of endoscopic severity was done from the most inflamed part of the bowel. The extent of disease was recorded as rectosigmoiditis, left-sided colitis, and pancolitis. Patients with severe hepatic, renal and cardiac disease were excluded from the study.

Healthy control subjects were visitors in the outpatient clinic of Haematology Department and had no known diseases, or clinical or laboratory evidence of metabolic, neoplastic or inflammatory disease. They also had no history of thromboembolic disease.

All patients and control subjects gave their informed consent to participate in the study, which was approved by the Hospital's Scientific Committee.

Laboratory studies

Blood samples were collected at baseline from UC patients and control subjects for the quantitative determination of von Willebrand factor antigen (vWF_{Ag}) in plasma with an immuno-turbidimetric assay (STA-Liatest vWF, Diagnostica Stago, France; normal values 50-160%). Additional blood samples were obtained from UC patients in order to determine variables of inflammation (ESR, CRP and fibrinogen) and parameters reflecting thrombin generation (thrombin-antithrombin complex [TAT], prothrombin fragments 1+2 [F1+2], and D-dimers [D-Di]).

ESR was measured by standard laboratory technique (normal values < 20 mm/h) and CRP was measured with ELISA (normal values < 5 mg/L). Plasma fibrinogen concentration was measured by the Claus method using bovine thrombin (bioMerieux sa, France) on OPTION coagulation analyzer (normal values 2-4 g/L).

TAT levels in plasma were measured by sandwich enzyme immunoassay (Enzygnost TAT micro, Dade Behring, Marburg, Germany; normal values 1-4.1 $\mu\text{g/L}$). F1+2 levels in plasma were measured by sandwich enzyme immunoassay (Enzygnost F1+2 micro, Dade Behring, Marburg, Germany; normal values 0.4-1.1 nmol/L). D-dimers levels in plasma were measured by immuno-turbidimetric assay (STA-Liatest D-Di, Diagnostica Stago, France; normal values < 500 $\mu\text{g/L}$).

All venipunctures were performed using a butterfly 18-gauge needle between 08:00 and 10:00 a.m. The first 10 mL of blood was not used for determination of hemostatic variables. Venous blood samples for hemostatic variables were collected in trisodium citrate tubes and platelet-poor plasma was prepared by one-stage centrifugation at 2 000 r/min for 20 min at 4 °C. Plasma was removed and assayed immediately for fibrinogen and stored at -20 °C until assayed, within one month, for vWF, TAT, F1+2, and D-dimers.

All UC patients were considered to have increased acute-phase reactants (APRs) if an increase in at least one of the two inflammation variables (ESR, CRP) was noted, as previously described^[26]. Likewise, all UC patients were considered to have increased coagulation markers (COAGs) if an increase in at least one of the three hemostatic variables (TAT, F1+2, and D-dimers) was noted.

Treatment and course

Patients with active UC were treated for attenuation of disease activity with high-dose corticosteroids and mesalazine orally and rectally. Azathioprine was continued if already used. Patients were set into a follow-up program with regular visits every 2nd wk for 12 wk. Corticosteroids were tapered off with a weekly based schedule throughout the study period. At the end of the study (12th wk), complete clinical, endoscopic and laboratory evaluation, similar to baseline week, was performed in all patients with active colitis. Complete response to therapy (remission) was considered, if a SCCAI score of ≤ 2 and endoscopic remission was achieved after 12 wk of therapy. Partial response was considered if a 50% reduction of SCCAI score was noted together with a reduction of endoscopic activity by at least one grade.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows package (version 11.0, SPSS, Chicago, IL, USA). Data were presented as mean \pm SD. Baseline comparisons were performed between the three main groups (healthy controls, patients with inactive UC and patients with active UC). A detailed analysis and multiple comparisons were performed between different subgroups of patients with UC according to disease activity, raised APRs or raised COAGs. Comparisons between groups were performed with Student's *t* test or ANOVA when appropriate. Student's *t* test for paired samples was used to compare baseline and follow-up measurements in patients with active disease. Associations between continuous variables were tested with Pearson's correlation. Differences in frequencies were studied with Fisher's exact test. $P < 0.05$ was considered statistically significant.

RESULTS

During baseline evaluation, 12 patients with ulcerative colitis were found to be in remission and 34 patients had ac-

Table 1 Demographic and clinical data of ulcerative colitis patients (mean \pm SD)

	Active UC (<i>n</i> = 34)	Inactive UC (<i>n</i> = 12)
Male/female	22/12	8/4
Age (yr)	41.5 \pm 14.6 (17-73)	42.8 \pm 15.2 (18-65)
Extent of disease		
Rectosigmoiditis	6	3
Left-sided colitis	20	6
Pancolitis	8	3
SCCAI score	8 \pm 3 (3-12)	0 \pm 1 (0-2)
Endoscopic score	16 \pm 2 (12-18)	2 \pm 1 (0-3)
Treatment		
Oral steroids	15	0
5-ASA compounds	30	12
Azathioprine	11	2
None	2	0
Smoking	7	5

SCCAI: simple clinical colitis activity index; 5-ASA: 5-aminosalicylates.

tive disease. Demographic and clinical data of patients are shown in Table 1. There were no significant differences in sex, age and extent of disease between patients with active and inactive disease.

Elevated plasma vWF concentrations were found in 1 patient with ulcerative colitis in remission and in 11 patients with active disease. None of the healthy subjects had an elevated value of plasma vWF. Mean plasma vWF concentrations were significantly higher in active ulcerative colitis patients (143.38 \pm 63.73%) than in healthy controls (100.75 \pm 29.65%, $P = 0.001$) and inactive UC patients (98.92 \pm 43.6%, $P = 0.031$). There was no difference in mean plasma vWF concentrations between HC and inactive UC patients (Table 2).

Mean levels of ESR, CRP and fibrinogen were significantly higher in active UC patients than in inactive UC patients. There were no significant differences in plasma levels of coagulation markers (D-dimers, F1+2 and TAT) between patients with active and inactive UC (Table 2).

UC patients with raised APRs ($n = 34$), irrespective of disease activity, had significantly higher mean plasma vWF levels than those with normal APRs ($n = 12$) (144.3 \pm 62.4% *vs* 96.2 \pm 45.8%, $P = 0.019$). Mean plasma vWF levels were also higher in UC patients with raised COAGs ($n = 27$), irrespective of disease activity, than in those with normal COAGs ($n = 19$), but did not reach statistical significance (141.3 \pm 64.8% *vs* 118.2 \pm 56.3%, $P = 0.216$). However, when all UC patients were divided into four subgroups according to raised or normal APRs and COAGs,

Table 2 Acute phase reactants and coagulation factors in patients with ulcerative colitis and healthy controls (mean \pm SD)

	Active UC (<i>n</i> = 34)	Inactive UC (<i>n</i> = 12)	Healthy controls (<i>n</i> = 52)
vWF (%)	143.38 \pm 63.73 (49-278)	98.92 \pm 43.6 ^a (25-188)	100.75 \pm 29.65 ^b (51-160)
ESR (mm/h)	40 \pm 21 (10-97)	16 \pm 12 ^a (4-40)	
CRP (mg/L)	24.7 \pm 40.2 (3.1-175.5)	4.1 \pm 1.7 ^a (3.1-7.3)	
Fibrinogen (g/L)	4.86 \pm 1.21 (2.93-7.3)	3.48 \pm 1.14 ^a (1.25-5.61)	
D-dimers (μ g/L)	873 \pm 1 308 (32-3 993)	608 \pm 1 149 (19-4 038)	
F1+2 (nmol/L)	3.71 \pm 6.09 (0.21-22.53)	3.72 \pm 6.41 (0.28-21.52)	
TAT (μ g/L)	6.91 \pm 15.18 (0.09-85.9)	3.99 \pm 4.2 (0.85-13.2)	

vWF: von Willebrand factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; F1+2: prothrombin fragments 1+2; TAT: thrombin-antithrombin complexes. ^a $P < 0.05$ active UC *vs* inactive UC. ^b $P < 0.001$ active UC *vs* HC.

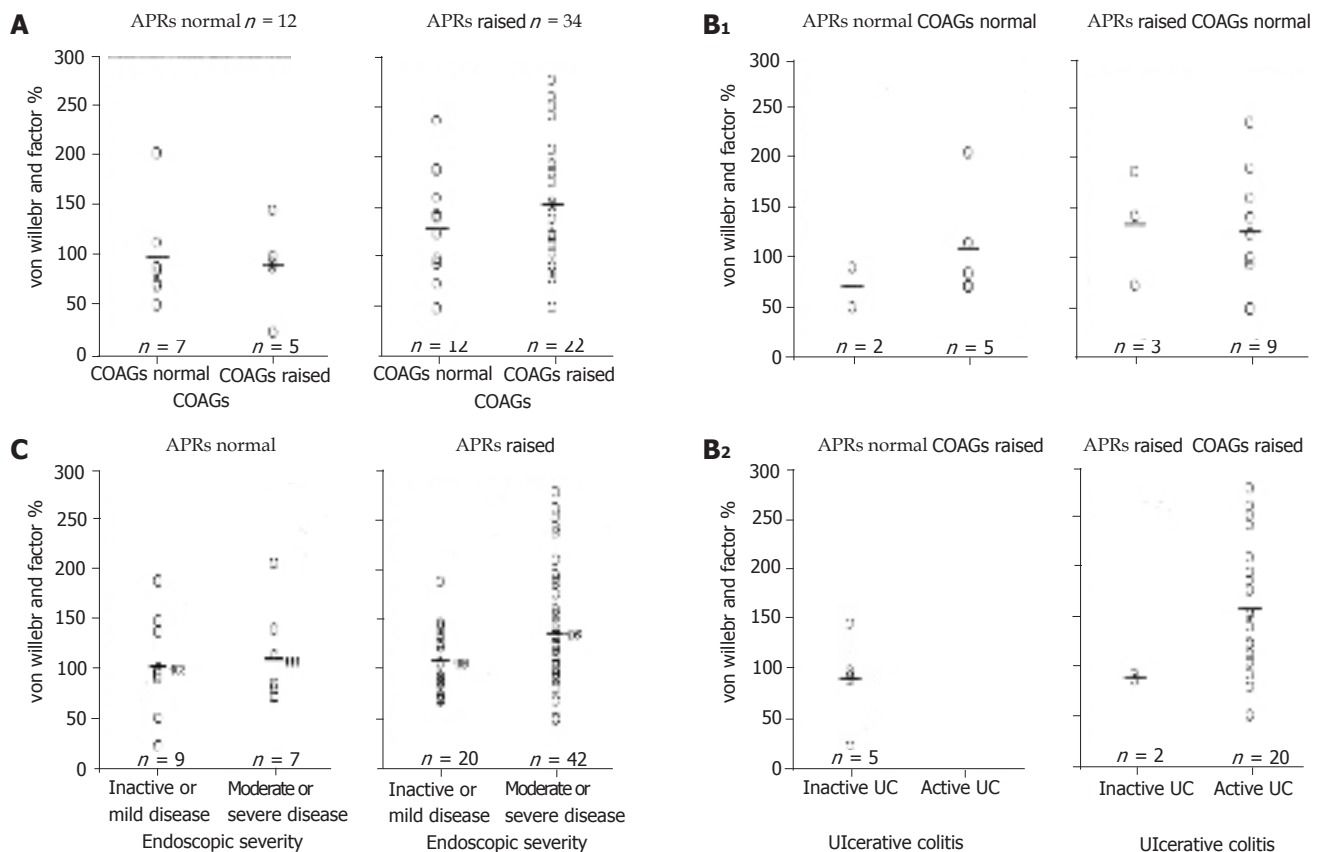


Figure 1 Mean plasma von Willebrand factor (vWF) levels in UC patients (A), their subgroups were divided according to disease activity, APRs and COAGs (B1, B2), as well as according to endoscopic severity and APRs (C). Open circle black dots (o) represent individual values and horizontal black lines (-) represent mean values. APRs: acute-phase reactants; COAGs: thrombin generation coagulation markers.

irrespective of disease activity, it was noted that patients with raised APRs had significantly higher mean plasma vWF levels than those with normal APRs, regardless of COAGs status (Figure 1A).

Furthermore, when UC patients were divided into subgroups according to disease activity and raised or not APRs and COAGs, there was a trend towards higher mean plasma vWF levels in almost all subgroups of patients with raised APRs (especially to those with active disease) compared to the patients with normal APRs. However, there were no significant differences between subgroups (Figure 1B1, B2).

In patients with ulcerative colitis (active and inactive), Pearson's correlation analysis revealed that there was a significant positive correlation of plasma vWF levels with clinical activity index (SCCAI) ($r = 0.41$, $P = 0.004$), endoscopic score ($r = 0.3$, $P = 0.041$), ESR ($r = 0.39$, $P = 0.006$), fibrinogen ($r = 0.42$, $P = 0.003$) and D-dimers ($r = 0.36$, $P = 0.015$). No correlation was noted between plasma vWF levels and extent of the disease or smoking status.

In all patients with UC, analysis of the percentages of high plasma vWF levels between subgroups revealed that raised APRs were the main factors influencing the plasma vWF levels (data not shown).

Thirty-two patients with active UC completed the study after 12 wk of treatment. Two patients did not show up at

the final date of the follow-up schedule (12th week). There were no complications of the disease or adverse events from the treatment during the study period. Twenty-two patients showed response to therapy (complete or partial) and 10 patients were non-responders. A significant decrease of the inflammatory parameters (fibrinogen and ESR), the coagulation markers (F1+2 and D-dimers) and von Willebrand factor levels was noted only in the "responders" group (Table 3).

We pooled all patients in respect of endoscopic severity, before and after the therapy for active disease plus patients in remission at baseline week, and found that mean plasma vWF levels in patients with active disease at endoscopy ($n = 54$, $131.2 \pm 56.2\%$) were significantly higher than those in patients with endoscopic remission ($n = 24$, $103.1 \pm 36.7\%$, $P = 0.028$). There were no significant differences in plasma vWF levels between the groups of endoscopic severity grades (mild to severe) in patients with active disease. However, when we divided the patients in respect of APR status, we found that patients with raised APRs and moderate or severe endoscopic activity had significantly higher mean plasma vWF levels than the other subgroups (Figure 1C).

DISCUSSION

This study showed that mean plasma vWF levels were significantly raised in patients with active UC compared

Table 3 Laboratory parameters at baseline and after 12 wk of therapy in active UC patients who completed the study ($n = 32$) (mean \pm SD)

	Weeks of follow-up	Responders	Non-responders
	Paired samples <i>t</i> test	$n = 22$	$n = 10$
ESR (mm/h)	Baseline	43 \pm 24	34 \pm 13
	12 th week	32 \pm 18	27 \pm 12
	<i>P</i>	0.055	0.206
CRP (mg/L)	Baseline	27.21 \pm 42.13	22.24 \pm 41.2
	12 th week	11.11 \pm 25.57	11.42 \pm 13.29
	<i>P</i>	0.106	0.460
Fibrinogen (g/L)	Baseline	4.9 \pm 1.13	4.98 \pm 1.48
	12 th week	4.05 \pm 0.68	4.55 \pm 0.82
	<i>P</i>	0.001	0.372
vWF (%)	Baseline	153.91 \pm 69.53	129.3 \pm 50.35
	12 th week	111.14 \pm 30.65	105.4 \pm 32.87
	<i>P</i>	0.005	0.153
F1+2 (nmol/L)	Baseline	3.73 \pm 5.73	4.21 \pm 7.26
	12 th week	1.23 \pm 1.12	0.71 \pm 0.26
	<i>P</i>	0.043	0.186
D-dimers (μ g/L)	Baseline	1 202 \pm 1 522	302 \pm 329
	12 th week	251 \pm 288	683 \pm 1 286
	<i>P</i>	0.005	0.381
TAT (μ g/L)	Baseline	4.39 \pm 4.6	13.43 \pm 26.94
	12 th week	5.41 \pm 13.1	1.97 \pm 1.57
	<i>P</i>	0.733	0.211

vWF: von Willebrand factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; F1+2: prothrombin fragments 1+2; TAT: thrombin-antithrombin complexes.

to healthy controls and patients with UC in remission. Since elevated circulating von Willebrand factor levels are regarded as markers of both endothelial dysfunction and acute phase response to inflammation, we tried to investigate the relationship between vWF and markers of inflammation and coagulation, in order to clarify the meaning of elevated vWF levels in our patients with active ulcerative colitis. APRs were significantly higher in patients with active UC than in those with inactive disease. On the other hand, there were no significant differences in markers of thrombin generation between patients with active and inactive UC (Table 2). These observations are in accordance with previous studies, suggesting that a hypercoagulable state exists in both active and inactive UC^[29-31]. In contrast, intense inflammatory response to elevated APRs is a prominent feature of active UC^[32,33].

In our study, UC patients were divided into subgroups according to disease activity (active and inactive) and APRs or COAGs status (raised or not). The analysis of data revealed two main findings. The mean plasma vWF levels were significantly higher in patients with active disease (Table 2) and higher in patients with raised APRs irrespective of disease activity or COAGs status (Figure 1).

In a recent study, Meucci *et al.*^[26] reported that elevated vWF levels in a group of patients with IBD are related to increased APRs, regardless of disease activity and concluded that elevated plasma vWF levels are a secondary manifestation due to systemic inflammation. In our study, we had similar findings with Meucci *et al.*^[26], suggesting that elevated plasma vWF levels in patients with UC correlate mainly with the inflammatory response and to a lesser degree with hypercoagulability. However, in the most recent study, Xu *et al.*^[25] had the opposite findings in a group of patients with UC, reporting that plasma vWF levels are

significantly higher in patients with ulcerative colitis than in controls, with no differences between active and inactive disease. They also reported that D-dimers levels are higher in patients with active disease than in those in remission and D-dimers levels are positively correlated with vWF levels. The authors concluded that elevated vWF levels both in active and inactive UC reflect the fact that endothelial cell damage is a feature of UC and that D-dimers levels can be used as a marker of inflammation to distinguish active from inactive UC.

Inflammation, coagulation and endothelial dysfunction correlations have been studied in many other clinical conditions^[34-37]. Inflammation as measured by CRP has been found to be associated with prothrombotic status and endothelial dysfunction as reflected by elevated vWF in acute coronary syndromes^[38]. Plasma vWF has been reported as an APR in patients with acute infectious diseases which parallels CRP levels during illness and recovery phase^[21]. The inflammatory and coagulation abnormalities observed in patients with ulcerative colitis possibly represent combined and cross-linked manifestations of the inflammation and coagulation systems, which are interrelated in a bidirectional way with the endothelium being the interface between inflammation and coagulation^[18].

Inflammation is undoubtedly a key component in the pathogenesis of ulcerative colitis^[39] and proinflammatory cytokines (IL-1, IL-6, IL-8, TNF- α , and IFN- γ) operate as a cascade and network in stimulating the production of acute-phase proteins and induction of acute-phase manifestations^[40]. Inflammation can also lead to activation of coagulation system with the endothelium playing a central role in all major pathways involved in the pathogenesis of hemostatic derangement^[18]. Proinflammatory cytokines induce a procoagulant profile with thrombin production,

through their effects on the vascular endothelial cells^[18] and can also stimulate vWF secretion from Weibel-Palade storage granules of the endothelial cells^[19,41,42]. A small fraction of the elevated plasma vWF levels can also be derived from platelets, since reactive thrombocytosis and *in vivo* activation of platelets are observed in active ulcerative colitis^[15], consisting acute-phase phenomena due to systemic inflammation^[40], but it seems that the contribution of platelet-derived vWF to elevated plasma levels is minor^[23]. We can assume that, like other coagulation factors which are synthesized in liver cells and behave as acute-phase proteins (fibrinogen, factor VIII) during inflammation, elevated plasma vWF concentrations represent an endothelial component of the acute-phase response^[23].

Glucocorticoids are known to increase plasma concentrations of factor VIII (FVIII) and von Willebrand factor (vWF), and their administration is associated with an increased thrombotic tendency^[43,44]. In our study, patients with active ulcerative colitis were treated with high doses of corticosteroids for attenuation of disease activity and had no thromboembolic complications during the study period. Follow-up measurements after 12 wk of treatment showed that patients who responded to therapy had a significant improvement of all the variables of inflammation and hemostasis, including von Willebrand factor. Inflammation is undoubtedly the main feature of UC and the attenuation of inflammatory process due to the potent anti-inflammatory properties of corticosteroids is the principal mechanism that contributes to the improvement of disease severity and its clinical or laboratory manifestations. It is likely that hepatic and endothelial acute-phase responses have a parallel course during inflammatory process since they may be regulated in a similar manner by the same cytokines.

In our study, we investigated the relationship of plasma vWF levels with disease activity, parameters of inflammation and hemostasis in a group of patients with ulcerative colitis (active and inactive), before and after therapy. It is the first study to our knowledge which combines the assessment of all these variables in a time course manner and represents an extension of the two most recent studies^[25,26]. The small number of patients in our study did not allow us to generalize our findings and give a possible explanation for any discrepancies of data among all relative studies. However, the general trend from the data is that plasma vWF levels are correlated with systemic inflammation.

In conclusion, increased plasma vWF levels in ulcerative colitis patients correlate with disease activity and increased acute-phase proteins. It seems that elevated plasma vWF levels in active ulcerative colitis patients reflect an acute-phase response of the perturbed endothelium due to inflammation and von Willebrand factor can be regarded as an endothelial APR. Further and larger studies are needed to show if plasma von Willebrand factor levels can be a useful and sensitive marker of disease activity or response to therapy.

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