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Original Article

Coagulation parameters in inflammatory bowel disease

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Abstract: Thromboembolic events represent a major cause of morbidity and mortality in patients with inflammatory bowel disease and they may occur both at the gastrointestinal tract and at extraintestinal sites. This study aimed to examine the alterations in coagulation parameters involved at different steps of hemostasis in patients with Crohn's disease and ulcerative colitis, in comparison with healthy individuals. Fifty-one patients with inflammatory bowel disease and 26 healthy controls were included in this study. Plasma levels of PT, APTT, AT III, plasminogen, fibrinogen, D-dimer, factor V, factor VIII, protein C, protein S, and APCR were measured and factor V Leiden mutation was examined in both patients and controls. Two patients with ulcerative colitis had a history of previous thromboembolic event. Inflammatory bowel disease was associated with significantly higher levels of fibrinogen, PT, factor V, factor VIII, plasminogen and thrombocyte. Protein S, fibrinogen, plasminogen and thrombocyte levels were associated with disease activity, depending on the type of the disease (Crohn's disease or ulcerative colitis). The coagulation abnormalities detected in this study seems to be a secondary phenomena resulting from the disease process, which is more likely to be associated with a multitude of factors rather than a single abnormality.

Keywords: Inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, coagulation

Introduction

Inflammatory bowel disease is a group of disorders associated with chronic, recurrent, and immune system-mediated inflammation of the bowel mucosa [1]. The reported global incidence and prevalence rates for ulcerative colitis vary between 1.2-20.3 and 6-246 per 100 000 persons, respectively, and the corresponding figures for Crohn's disease are 0.03-15.6 and 3.6-214 [2]. In a population based cohort study involving 1160 patients with ulcerative colitis, the complication-related mortality rate was 9.6% during a follow-up period of 35 years, [3] in another study, 221 patients with Crohn's disease were followed up for 33 years, with an overall complication-related mortality rate of 7.7% [4].

Of the extra-intestinal manifestations of inflammatory bowel disease (IBD), thromboembolic events represent a major cause of morbidity and mortality [5] with a 3.6 times increased risk in comparison with the general population [6]. Although clinical observations suggest an incidence rate between 1 and 8% for thromboembolic events in subjects with IBD, [5-7] postmortem studies point out to a much higher occurrence rate around 41% [8]. As a matter of fact, these and similar findings have led to an increased interest in the search for the association between IBD and hypercoagulable states as a potential cause of increased morbidity and mortality due to thromboembolic events in IBD [5, 9]. For instance, the existence of documentable prothrombotic abnormalities and a positive history for thromboembolic complications

were demonstrated in at least one third of the subjects with IBD in a study by Solem et al [9].

Thrombotic events in subjects with IBD are not exclusively confined to the gastrointestinal tract, and they may occur at extraintestinal sites as well [7, 10]. Studies examining the underlying mechanisms responsible for the hypercoagulable states in IBD have provided varying results [11-14] and generally suggest that almost all components of hemostasis such as platelets, fibrinolysis, and the coagulation cascade are involved in its pathogenesis [15]. Obviously, more research is warranted to elucidate this complex interplay between etiological factors.

Therefore, we aimed to examine the alterations in coagulation parameters involved at different steps of hemostasis as possible causes of thromboembolism in patients with IBD. In this comparative study, the following coagulation parameters in ulcerative colitis patients, Crohn's disease patients, and normal individuals were assessed: antithrombin III (AT III), protein C, protein S, factor V, factor VIII, fibrinogen, plasminogen, D-dimer, prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, and activated protein C resistance (APCR).

Material and methods

Subjects

In total, 51 patients with inflammatory bowel disease (27 males, 24 females) and 26 healthy controls (10 males, 16 females) were included in this study. Diagnosis of inflammatory bowel disease was based on clinical, endoscopic, histological, radiological and microbiological criteria. Excluding criteria were as follows: severe hepatic or renal insufficiency, proteinuria, malnutrition, valvular disease, atrial fibrillation, pregnancy, immobilization, recent surgical intervention, and oral contraceptive, anticoagulant or heparin use. The study was approved by local ethics committee and conducted in accordance with declaration of Helsinki. All patients provided informed consent prior to study entry.

Assessments

Disease activity was assessed using Truelove-Witts criteria [16] in patients with ulcerative colitis and they were categorized as having active or inactive disease. Crohn's disease severity was evaluated using Crohn Disease Activity Index (CDAI) [17] where a score <150 was considered inactive disease and a score >220 was an indication of active disease.

In addition to medical history and a thorough physical examination, all IBD patients underwent chest X-ray, lower extremity Doppler USG and abdominal Doppler USG examinations to identify any evidence of thromboembolism.

Laboratory measurements

Venous blood samples were collected from all study participants, placed in tubes containing 3.8% trisodium citrate, centrifuged at 2000 rpm and 4°C for 10 minutes, and plasma was separated. Samples that were not immediately assessed were kept at -20°C until the time of assessment. Plasma levels of PT, aPTT, AT III, plasminogen, fibrinogen, D-dimer, factor V, factor VIII, protein C, protein S, and APCR were measured and factor V Leiden mutation was examined.

Statistical analysis

SPSS (Statistical Package for Social Sciences) version 17.0 was used for the analysis of data. Data are presented as mean ± standard deviation and frequency. Continuous variables were compared using student t test for independent samples or Mann-Whitney U test, depending on the distribution of data. Categorical data were compared using chi-square test. A p value <0.05 was used as the indication for statistical significance.

Results

Patients

Among patients, 33 (20 males, 13 females) had ulcerative colitis (64.7%) and 18 (7 males, 11 females) had Crohn's disease (35.3%). The mean ages of patients and controls were 40.7±6.92 and 36.2±5.47 years, respectively, with no significant difference. Gender distribution was similar in patients and controls. However, the mean age of ulcerative colitis were significantly higher when compared to the patients with Crohn's disease (46.8±6.76 vs.

Table 1. Comparisons of coagulation parameters between patients and controls

Parameter	Control (n = 26)	IBD (n = 51)	P (control vs. IBD)	UC (n = 33)	P (UC vs. control)	Crohn (n = 18)	P (Crohn vs. control)	P (UC vs. Crohn)
Protein C, %	104.3±9.32	92.2±8.94	0.073	91.7±10.74	0.196	97.6±9.9	0.406	0.976
Protein S, %	78.6±10.26	76.2±6.71	0.718	63.3±7.59	0.959	63.0±6.35	0.428	0.271
AT III, %	112.6±9.53	105.9±10.49	0.088	96.7±8.32	0.058	105.9±9.9	0.731	0.405
Fibrinogen, mg/dL	322.9±27.42	439.2±21.21	<0.001	446.0±21.48	0.016	485.5±22.03	<0.001	0.249
D-Dimer, g/L	245.0±18.97	275.4±16.58	0.288	264.6±12.09	0.517	249.3±11.8	0.797	0.948
PT, sec	11.6±0.94	12.3±0.91	0.035	12.6±1.14	0.026	12.5±0.84	0.455	0.510
aPTT, sec	32.6±6.54	34.6±5.92	0.131	35.9±5.99	0.143	33.8±4.79	0.908	0.415
Factor V, %	89.0±8.21	109.3±10.45	0.002	111.6±10.56	0.008	108.0±10.39	0.069	0.918
Factor VIII, %	92.3±7.84	117.4±11.05	0.026	117.8±11.27	0.012	112.8±9.98	0.122	0.824
APCR, sec	0.95±0.39	0.98±0.34	0.670	0.95±0.21	0.688	1.0±0.37	0.839	0.988
Plasminogen, %	97.7±8.98	107.2±10.35	0.043	101.3±8.2	0.409	121.1±9.54	0.029	0.257
Thrombocyte, mm^3 (×1000)	247±16.97	403±20.12	<0.001	438±15.19	0.004	510±22.58	<0.001	0.206

IBD, inflammatory bowel disease; UC, ulcerative colitis; AT III, antithrombin III; PT, prothrombin time; aPTT, activated partial thromboplastin time; APCR, activated protein C resistance.

29.4±4.83 y, p<0.001). On the other hand, gender distribution (p = 0.159) and disease duration (4.97 vs. 6.44 y, p = 0.475) were similar in ulcerative colitis and Crohn's disease patients. Two patients with ulcerative colitis had a history of previous thromboembolic event: acute MI occurring at the age of 25 when in remission and one deep vein thrombosis at the age of 28 during active disease. Thus, the prevalence of thromboembolic events was 6.06% for ulcerative colitis and 3.92% for inflammatory bowel disease in general.

Coagulation parameters in inflammatory bowel disease

Comparisons of coagulation parameters between patients and controls are shown in **Table 1**. Inflammatory bowel disease was associated with significantly higher levels of fibrinogen, PT, factor V, factor VIII, plasminogen and thrombocyte. Although thrombocyte and fibrinogen levels were increased in both ulcerative colitis and Crohn's disease patients, PT, factor V and factor VIII levels were only increased in ulcerative colitis. Plasminogen on the other hand, was only increased in Crohn's disease. Factor V Leiden mutation was present in 1.96% (n = 1), 16.66% (n = 3), and 3.84% (n = 1) in ulcerative colitis patients, Crohn's disease patients, and controls, respectively. The corresponding rate was 7.84% (n = 4) in the combined inflammatory bowel disease group. Groups did not differ with regard to the frequency of factor V Leiden mutation.

The association between disease activity/ medication and coagulation parameters

Active inflammatory bowel disease was not associated with significantly different levels of protein C, APCR, factor V, factor VIII, AT III, D-Dimer, PT, and aPTT, when compared to patients in remission. However, protein S, fibrinogen, plasminogen and thrombocyte levels were associated with disease activity. Active ulcerative colitis disease was associated with significantly higher thrombocyte (438 vs. 247×1000, p = 0.0003) and fibrinogen (446.0 vs. 322.9 mg/dL, p = 0.030) levels when compared to controls; however, such an association was not present for the ulcerative colitis patients in remission. On the other hand, active Crohn's disease was associated with significantly higher plasminogen (112.9 vs. 97.7%, p = 0.015), thrombocyte (451 vs. 247×1000, p = 0.002) and fibrinogen (478.1 vs. 322.9, p = 0.031) levels compared to controls. The same relation was only true for thrombocyte levels, with significantly higher figures in Crohn's disease in remission (393 vs. 247×1000, p = 0.011); however, plasminogen and fibrinogen levels did not differ significantly between patients in remission and controls. The levels of all coagulation parameters were similar in patients receiving immunosuppressant therapy and patients receiving only aminosalicylates.

Discussion

Absence of increased risk of thromboembolism in other chronic inflammatory conditions such

as rheumatoid arthritis and celiac disease lends a unique position to IBD in terms of hemostatic risk [6, 18]. In this regard, it is remarkable to note that thromboembolic events represent the most frequent cause of intensive care unit admissions in subjects with IBD [19]. Furthermore, thromboembolic events tend to occur at a younger age in IBD patients [19, 20]. Therefore, coagulation parameters in IBD patients were examined in order to shed some light on the etiological factors responsible for the development of thromboembolic events in IBD on the basis of the assumption that such information may help reduce morbidity and mortality associated with this condition.

Platelets are involved in the first step of thrombus formation and abnormal platelet function is an established cause of hypercoagulation [21]. One of the main findings of our study is the detection of significantly higher platelet counts in the overall IBD, active IBD and remission-Crohn's disease groups, in line with some other previous research [5, 11, 13, 14]. The mechanisms responsible for the increased platelet count in IBD are not very well understood and have usually been explained on the basis of a non-specific inflammatory reaction [22]. Thrombocytosis reflects a disruption in the process of thrombopoiesis which might be related to increased plasma levels of thrombopoietin and interleukin-6 (IL-6), both of which are responsible for the megakaryocytic maturation. In vitro studies showed the presence of spontaneous aggregation of platelets irrespective of disease severity in more than 30% of the patients with IBD [22]. Also, some researchers proposed the use of increased platelet count as a potential marker of disease activity in IBD in addition to the traditional inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate [23].

Fibrinogen is an acute phase reactant that plays a role in the formation of thrombi and its concentration increases in the presence of inflammation. High plasma fibrinogen levels are associated with increased plasma viscosity and platelet activation, as well as comprised microcirculation of the inflamed bowel [24]. In the present study a significantly higher fibrinogen level was determined in IBD, ulcerative colitis, Crohn's, active ulcerative colitis, and active Crohn's groups as compared to controls, similar to previous reports [13, 14, 25, 26].

Plasminogen is a major component of the fibrinolytic system which is converted into plasmin by tPA (tissue-type plasminogen activator) and urokinase plasminogen activator and inhibited via the action of PAI-1 (plasminogen activator inhibitor), PAI-2, and antiplasmin [26]. In our study subjects, significantly higher plasminogen levels were detected in IBD, ulcerative colitis, and active Crohn's groups. It is noteworthy to observe that the role of plasminogen as a coagulation factor in patients with IBD has been the subject of relatively few publications. In a study by Kume et al found an insignificant increase in plasminogen levels in active and inactive ulcerative colitis [25] similar to Alkim et al who did not observe any differences between controls and subjects with IBD, active or inactive IBD, ulcerative colitis, or Crohn's disease [26] Increased plasminogen levels appear to be associated with fibrinogen, since fibrinogen and plasminogen levels were particularly higher in Crohn's disease patients as compared to controls and ulcerative colitis patients.

Factors V and VIII play a role in the common coagulation pathway, which is initiated by the extrinsic and intrinsic pathways. Despite significantly higher levels of factor V and VIII in IBD and ulcerative colitis patients in comparison with controls, there were no significant differences between active disease and remission groups. While some of the previous studies reported increased factor V and VIII levels in IBD, [5, 11] others found no such differences between IBD and controls [14, 26]. The study by Kume et al. detected higher factor V and VIII levels in active ulcerative colitis patients vs. those with inactive disease [25].

PT is a marker for the extrinsic pathway, which comprises the first step of the coagulation system. Significantly prolonged PT values were detected among IBD and ulcerative colitis patients in this study as compared to controls. In Alkim et al.'s study, active IBD patients had prolonged PT values than controls and inactive IBD patients, [26] similar to Lam et al who reported prolonged PT in IBD patients [11]. On the other hand, some other studies found no difference in PT between IBD and controls [14, 25].

AT III is a plasma coagulation inhibitor known to decrease in IBD [15, 23, 27, 28]. It triggers heparin secretion by mast cells. Kume found higher levels in active ulcerative when compared to inactive disease [25]. In contrast, the present study did not find a difference with regard to disease activity.

D-dimer is a fibrin degradation product and its increase is associated with a tendency for thrombus production in the vessels, thus potentially increasing the risk for deep vein thrombosis, pulmonary embolism and disseminated intravascular coagulation. Kume found increased levels in active ulcerative colitis when compared to patients with inactive disease [25]; and Alkim found higher levels in IBD when compared to healthy controls [26]. A recent study found that fibrin clots increase D-dimer secretion in patients with IBD [29]. Nguyen et al. found a high prevalence of elevated D-dimer in patients with IBD but without deep venous thrombosis, limiting its use in this group of patients [30]. Our study however, did not find a difference between groups with respect to D-dimer levels, which may be attributed to the low number of patients.

Although several studies showed reduced levels of protein C in patients with IBD when compared to healthy controls [11, 14], this study, in line with two other studies [25, 26], failed to find a difference.

Our patients with active ulcerative colitis had significantly lower protein S levels than inactive ulcerative colitis patients. Protein S is involved in the thrombin formation. Previously, Alkim et al observed lower protein S levels in active IBD than in inactive IBD and controls [26] as opposed to Kume et al who did not detect any differences in protein S levels between active and inactive ulcerative colitis [25].

A major cause of hereditary thrombophilia is factor V Leiden mutation, the active form of which is associated with a resistance against the activated protein C (APC) referred to as APCR, the acronym standing for “activated protein C resistance”. In unselected cases of venous thrombosis, a prevalence rate of 20 to 30% was found for factor V Leiden mutations [23]. Our study revealed no differences in APCR and factor V Leiden mutations between the study groups. There is one published study which reported a prevalence rate of 28.5% for factor V Leiden mutation among IBD patients, [31] despite the absence of such difference in most others [32, 33].

Azathioprine and its active metabolite, 6-mercaptopurine, are the most frequently used immunosuppressants in IBD and their mechanism of action involves the induction of in vitro platelet aggregation through the inhibition of adenosine diphosphate, in addition to their well known effects on the immune system [34]. This may have an additional role in the pathogenesis of thrombosis in IBD. Infliximab, a direct chimeric monoclonal antibody against TNF-α, has been reported to normalize the hemostatic parameters [35]. A similar coagulation parameter profile was found in patients receiving immunosuppressants and in patients receiving aminosalicylates only.

In the present study, twelve coagulation parameters encompassing the whole range of processes involved in thrombus formation were assessed, in addition to a genetic parameter, factor V Leiden mutation. Although, there was an even distribution of patient and controls within the study groups, a larger sample size would certainly provide a more statistically valid set of results. Our literature search did not reveal any other studies that provided a similar comparison in terms of the medications received by IBD patients.

The difference between control subjects and patients was more marked in those with Crohn’s disease as compared to ulcerative colitis patients. The coagulation abnormalities detected among patients appeared to be secondary phenomena resulting from the disease process, which is more likely to be associated with a multitude of factors rather than a single abnormality. Thromboembolic events in IBD represent a latent prothrombotic inclination that may be associated with the inflammation characterizing these conditions.

Disclosure of conflict of interest

None.

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