INTRODUCTION

Thromboembolism is an extraintestinal manifestation and an important cause of morbidity and mortality in patients with inflammatory bowel disease (IBD).\(^1\)

The pathogenesis of thromboembolic complications in IBD is multifactorial and has not been fully elucidated yet. In patients with IBD, disbalance between procoagulant, anticoagulant, and fibrinolytic factors occurs that predisposes to the development of embolism in IBD. A number of genetic factors have been shown to increase the incidence of thromboembolic complications.

Moreover, numerous acquired factors have been confirmed to play a role here, including chronic immobilization, surgical procedures, central venous catheters, steroid therapy, oral contraceptives, cigarette smoking, hyperhomocysteinemia, vitamin deficiency, dehydration, and the inflammatory process itself.\(^1,2\)

There are 3 natural anticoagulation mechanisms that control blood clotting: the protein C (PC) anticoagulant pathway, tissue factor pathway inhibitor, and the heparin-antithrombin pathway. The PC pathway is initiated by thrombin attaching to its specific receptor on the platelet membrane. The receptor on the platelet cell surface is activated, leading to the release of the activated protein C (APC) from its zymogen form, protein C.

APC binds to its receptor, thrombomodulin (TM), on the surface of the endothelial cell, causing a conformational change in the receptor. The receptor-bound APC then cleaves factor Va and factor VIIIa, thereby inhibiting thrombin and activated factor X, respectively. An imbalance between procoagulant (e.g., thrombin) and anticoagulant (e.g., APC) factors can lead to the development of thromboembolic complications in IBD.

OBJECTIVES

The aim of the study was to assess the components of the PC system and their correlations with disease activity in patients with IBD.

PATIENTS AND METHODS

The levels of PC, free protein S (PS), and soluble thrombomodulin (sTM) were measured in 55 consecutive patients with ulcerative colitis (UC), 50 patients with Crohn’s disease (CD), and 41 healthy volunteers. Correlations between PC system components and disease activity, hemostatic variables, and inflammatory markers were assessed.

RESULTS

sTM levels in patients with UC were higher compared with controls (24.5 vs. 17.5 ng/ml; \(P = 0.0042\)). In patients with IBD, PC activity was higher and PS activity was lower compared with controls (\(P <0.001\)). Tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)) levels were higher in patients with IBD, and interleukin 6 (IL-6) levels were higher only in patients with CD. In patients with UC, a positive correlation was observed between sTM and both PC and PS levels \((r = 0.28\) and \(r = 0.34\), respectively, \(P <0.05\)). Only PC levels correlated with UC activity \((r = 0.3, P <0.05)\). No correlations of TNF-\(\alpha\), IL-6, and C-reactive protein with PC, PS, and sTM levels were observed.

CONCLUSIONS

The PC pathway is defective in patients with CD and UC. Hypercoagulability in IBD might be associated not only with the inflammatory process but also with disturbances in the anticoagulant system, since defective PC pathway was observed both in active and nonactive disease.
to thrombomodulin (TM) bound to the endothelium. Following its binding to TM, thrombin acquires the ability to activate PC. Activated PC (APC), in the presence of a cofactor, protein S (PS), inactivates active factors V and VIII.

It has been demonstrated that TM and APC, in addition to their anticoagulant properties, also affect the course of the inflammatory process, apoptosis, and endothelial barrier.\(^2\)\(^3\)

Clinical trials in patients with sepsis have shown that a decrease in PC levels correlates with severe sepsis.\(^4\) Moreover, PC administration in patients with meningococcemia decreases the symptoms of purpura fulminans and significantly increases survival rates.\(^5\)\(^6\) A decrease in TM levels has been found to be correlated with increased thrombosis and leukocyte infiltration,\(^7\) and its locally increased expression prevents the occurrence of arterial embolism in animal models.\(^8\)

The available reports on plasma TM levels in IBD patients provide conflicting results. Weber et al.\(^9\) and Remkova et al.\(^10\) demonstrated that higher TM levels occur only in patients with active Crohn’s disease (CD), but failed to demonstrate any changes in PC and PS levels in IBD. In another study published in 1997, TM concentrations were higher in active ulcerative colitis (UC) than in healthy controls.\(^11\)

To date, no comprehensive studies have been conducted on the presence of circulating TM, PC, and PS in IBD and their importance in the course of IBD. In view of the role of the PC pathway in hemostasis and its effect on inflammation, we sought to investigate the association between TM, PC, and PS levels and the activity of UC and CD in affected individuals.

**Patients and Methods**

**Study population**

The study enrolled 105 patients with IBD aged from 18 to 66 years, including 55 patients with UC (28 women) and 50 patients with CD (23 women). IBD was diagnosed based on the presence of clinical symptoms as well as endoscopic, radiological, and histopathological criteria.\(^12\) The control group included 41 healthy volunteers aged 18 to 60 years (19 women). The groups were presented and characterized in a previous paper by Owczarek et al.\(^13\) The inclusion and exclusion criteria were the same as in the previous study. The exclusion criteria were pregnancy, previous history of thrombosis, concomitant inflammatory disorders, concomitant severe diseases including cirrhosis, hepatitis, renal failure, cancer, and diabetes. Patients with a history of oral anticoagulants and contraceptives as well as patients taking corticosteroids in the last 3 months were also excluded.

Patients enrolled into the study were followed at the Department of Gastroenterology, Hepatology and Infectious Diseases, Jagiellonian University Medical College, Kraków, Poland. The study was approved by the Bioethics Committee of the Jagiellonian University. All participants gave their written informed consent to participate in the study.

**Clinical assessment**

In patients with IBD and in controls, the assessment included the presence of other diseases, cigarette smoking habits, current use of medications, and the measurement of the body mass index (BMI). In the CD and UC groups, disease activity, location, duration, as well as complications and past surgical procedures were determined.

Disease activity was assessed using the Crohn’s Disease Activity Index (CDAI) for CD and the Disease Activity Index (DAI) for UC. The CDAI combined the evaluation of vital parameters, clinical findings, and medical history as described in detail elsewhere.\(^14\) The DAI is a composite score based on the daily number of stools, visible blood in stool, appearance of the colonic mucosa at endoscopy, and the physician’s global assessment. Each variable scores from 0 to 3 points, so that the total index score ranges from 0 to 12.\(^15\)

The site of inflammatory lesions in CD and UC was determined according to the Montreal Classification of 2005.\(^16\) Complications were defined as the presence of an abscess, stenoses resulting in postobstructive symptoms, fistulas, and IBD-associated extraintestinal diseases.

Based on the CDAI score in patients with CD and the DAI score in patients with UC, the groups were subsequently divided into 2 subgroups: nonactive CD (CDAI <150) and active CD (CDAI ≥150), and nonactive UC (DAI <6) and active UC (DAI ≥6).\(^17\)

**Laboratory tests**

Blood samples were collected from the antecubital vein of each participant after a fasting period in the morning hours. On the same day, the following laboratory parameters were determined: white blood cell count, hematocrit, blood platelets (PLT), fibrinogen, C-reactive protein (CRP), activated partial thromboplastin time (APTT), D-dimer, and antithrombin. CRP was assayed using a Modular P clinical chemistry analyzer (Roche Diagnostics, Mannheim, Germany). Complete blood count was performed with a Sysmex XE-2100 hematology automated analyzer (Sysmex, Kobe, Germany). Fibrinogen and APTT were measured using the Behring Coagulation System (BCS, Dade Behring, Marburg, Germany). Antithrombin activity was measured using chromogenic assays (Siemens, Germany). Plasma D-dimer levels were measured using the VIDAS system (Roche, France).

Plasma was obtained from another blood sample, which was later used for determination of the PC system components (TM, PC, free PS) as well as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α). PC activity was measured using chromogenic assays (Siemens, Germany). Plasma soluble TM (sTM) concentrations were determined using an enzyme-linked immunosorbent essay (ELISA) kit (Asserachrom Thrombomodulin, Roche, France). Free PS levels were assayed...
RESULTS We observed no differences between patients with UC (men, 49.1%) and CD (men, 54.0%) and controls (men, 54.0%) with respect to sex. We observed statistically significant differences in median age between the CD and UC groups. Median and quartiles (Q1–Q3) were 36 (25–46) years and 29.5 (22–34) years in the UC and CD groups, respectively. Median BMI was markedly lower in patients with CD (20.51 [18.38–24.85] kg/m²) compared with controls (23.5 [21.45–26.28] kg/m²).

As for the clinical parameters, patients with CD had lower median value of disease duration than those with UC (3 [2–6] vs. 5 [2–9] years, respectively; P = 0.0366). Moreover, patients with CD had a higher number of complications (15 [30%] vs. 3 [5.45%], respectively; P = 0.0009) and underwent more surgical procedures (20 [40%] vs. 0 [0%], respectively; P < 0.0001).

The analysis of proinflammatory cytokines revealed statistically significantly higher medians of TNF-α in patients with UC (1.593 [1.136–3.601] pg/ml) and CD (1.719 [1.340–2.846] pg/ml) compared with controls (1.225 [0.951–1.566] pg/ml). Median IL-6 was significantly higher only in patients with CD (4.075 [1.685–5.858] pg/ml) compared with controls (1.70 [1.14–2.84] pg/ml).

The mean values of APTT and D-dimer in all groups were within normal ranges (APTT: UC, 33.32 ±5.0 s; CD, 34.07 ±4.0 s; controls, 36.42 ±4.2 s; D-dimer: UC, 258.43 ±211.4 ng/ml; CD, 222.82 ±138.6 ng/ml; controls, 288.05 ±82.7 ng/ml).

Mediand D-dimer values in the UC and CD groups were significantly lower than in controls (UC, 181 [115–342] ng/ml; CD, 194 [123–257] ng/ml; controls, 300 [210–340] ng/ml). A similar association was shown for APTT only in the UC group in comparison with controls (32.43 [29.62–35.40] s vs. 36.3 [32.8–39.4] s).

Median sTM was higher in the UC group than in controls (22.10 [40%] vs. 0 [0%], respectively; P = 0.0009; FIGURE 1).

Higher median values were demonstrated for PC activity in the UC and CD groups compared with controls (UC, 114.76 [99.86–137.58]%); CD, 113.38 [101.92–124.54]%; P < 0.001; controls: 96.98 [89.13–107.58]%; FIGURE 2).

In the UC and CD groups, the median values of free PS were lower compared with controls (UC, 81.81 [73.35–97.51]%; P = 0.003; CD, 70.14 [64.25–96.76]%); P < 0.001; controls, 107.24 [80.96–135.36]%; FIGURE 3).

The characteristics of patients with active and nonactive UC and CD are presented in TABLES 1 and 2.
No such correlations were shown for sTM and PS either in patients with UC or CD patients.

In the control group, male patients showed higher mean levels of sTM (19.83 ±7.4 ng/ml), PC (104.16 ±13.05%), and PS (127.99 ±34.75%) (P <0.01). In men with UC, only median sTM levels (23.47 [20.89–35.57] ng/ml), P < 0.01) and mean PC levels (127 ±29.61%, P < 0.05) were higher. In contrast, male patients with CD had higher mean PS levels (90.39 ±26.95%, P < 0.01). Medication regimens did not affect plasma sTM, PC, and PS levels. Other clinical variables, i.e., disease location and duration showed no significant association with plasma sTM, PC, and PS levels. Furthermore, no correlations between TNF-α, IL-6, CRP, or other inflammatory markers and PC, PS, sTM levels were observed. In controls, a positive correlation was demonstrated only between PC and PS levels.

**DISCUSSION** It is well-established that there is an increased risk of thrombosis in IBD, but the precise pathogenetic mechanism of thromboembolic complications in this disease has not

| Characteristics | Nonactive UC n = 24 | Active UC n = 31 | Control group n = 41 |
|-----------------|----------------------|------------------|---------------------|
| white blood cells, × 10³/µl | 6.5 ± 1.8 | 8.3 ± 3.2 a | 6.33 ± 1.8 |
| hematocrit, % | 41.8 ± 4.5 a | 38.7 ± 3.9 a | 42.18 ± 3.7 |
| platelet count, × 10³/µl | 254.5 ± 66.0 b | 332.6 ± 98.2 b | 215.61 ± 49.7 |
| CRP, mg/l | 3.0 ± 4.9 a a | 21.1 ± 23.3 a | 0.72 ± 0.5 |
| fibrinogen, g/l | 3.1 ± 1.2 a | 5.3 ± 1.9 a | 2.75 ± 0.5 |
| TNF-α, pg/ml | 1.8 ± 1.1 | 3.1 ± 2.9 a | 1.62 ± 1.3 |
| IL-6, pg/ml | 1.6 ± 1.1 a | 6.4 ± 5.2 a | 2.07 ± 1.2 |
| albumin, g/l | 44.6 ± 4.3 a | 39.6 ± 4.9 a | 46.10 ± 2.0 |
| APTT, s | 33.7 ± 4.9 | 33.1 ± 5.2 a | 36.30 ± 4.2 |
| D-dimer, ng/ml | 170.8 ± 106.3 a | 280.3 ± 207.0 | 288.05 ± 82.7 |
| TM, ng/ml | 24.8 ± 10.2 a | 24.4 ± 13.0 a | 17.47 ± 6.9 |
| PC, % | 111.1 ± 20.9 | 126.1 ± 30.46 b | 98.47 ± 14.6 |
| PS, % | 87.6 ± 25.0 a | 80.4 ± 19.6 a | 108.85 ± 34.8 |

Data are presented as mean ± SD. Median (lower and upper quartile) were added if the nonparametric test was used (i.e., Kruskal-Wallis). Otherwise, the one-way analysis of variance was used.

a P <0.05 compared with active UC
b P <0.05 compared with controls

Abbreviations: APTT – activated partial thromboplastin time, CRP – C-reactive protein, IL-6 – interleukin 6, SD – standard deviation, TNF-α – tumor necrosis factor α, others – see Figures 1 and 2.
been fully elucidated. Numerous research papers have reported qualitative and quantitative abnormalities in the hemostatic system. The results describing hemostatic parameters and thrombotic risk factors in IBD are conflicting and unclear. Controversies may result from the differences in the studied populations (demographic and clinical features, definition and evaluation of disease activity).19

Hemostasis is an indispensable component of an inflammatory process. During inflammation, not only proteases originating from inflammatory cells become activated, but also proteases belonging to coagulation and fibrinolytic systems.7

Activation of coagulation acts as a constituent of an inflammatory response by directly mediating cytokine responses, and some proinflammatory cytokines, such as IL-6 and TNF-α, activate coagulation.20 Indeed, deficiencies in the PC pathway components not only promote thrombosis, but also exacerbate the inflammatory process.21

We demonstrated higher mean sTM levels in patients with UC compared with controls. Weber et al.9 demonstrated a significant increase in serum TM values only in patients with CD. In contrast, Boehme et al.11 showed a significant increase in TM levels only in patients with UC, while several publications failed to demonstrate any differences in TM levels in IBD patients.22,23

A number of investigators reported higher levels of sTM with a simultaneous decrease in TM expression in the inflamed colonic mucosal microvessels.24,25 TM is a glycoprotein that is situated not only on the surface of the endothelial cells, but also on the surface of neutrophils, monocytes, platelets, astrocytes, keratinocytes, and mesothelial cells.21 TM is also present in a soluble form in plasma, generated by enzymatic cleavage of the intact protein.26 sTM maintains its anti-inflammatory and antiapoptotic functions, but does not have any antithrombotic properties.21

Additionally, the effect of proinflammatory cytokines on endothelial expression of TM was evaluated, demonstrating that TNF-α and interleukin 1β decreased the expression of TM and endothelial PC receptor (EPCR) through inhibition of transcription RNA and, at the same time, they improved detachment of free forms from cell surfaces.25 In IBD, an increase in proinflammatory cytokines is observed (especially TNF-α),27 which has been also confirmed in our study. In addition, we showed that in the subgroup of patients with
active CD, mean TNF-α levels are significantly higher compared with patients with nonactive disease, while no such association was shown for UC. This might explain the differences in TM levels between the active UC and CD subgroups.

While evaluating the associations of sTM in particular groups, we showed a positive correlation between sTM and PC and PS in the UC group, while no such correlation was observed in the CD group and controls.

Higher TM levels are observed in diseases associated with vascular endothelial damage, such as infections, sepsis, and inflammatory conditions. For this reason, increased TM is believed to be a marker of endothelial damage. Recent investigations which showed that plasma TM levels are inversely correlated with the development of coronary heart disease are particularly interesting. Based on this finding, it was concluded that sTM may play a vasoprotective role through its anti-inflammatory properties. Experimental models demonstrated that low sTM levels are associated with increased tumor proliferation. In addition, the results of studies on animal models employing sTM in inflammatory diseases are promising and lay the basis for further studies on the therapeutic use of sTM fragments in IBD among other diseases.

The present study showed higher mean PC levels in the active and nonactive CD subgroups and in the active UC subgroup compared with controls. However, no correlations between PC levels and disease activity or between PC levels and inflammatory markers were observed.

PC is a vitamin-K-dependent glycoprotein that is synthesized by the liver. It is transformed to APC by the thrombin-TM complex. APC then exerts its anticoagulant effect by binding PS and inactivating factors Va and VIIIa, thus inhibiting further thrombin generation. PS is produced in the liver and readily detectable in systemic circulation. In plasma, it is present in 2 forms: free and bound to the complement component, C4b-binding protein; only the free form demonstrates APC cofactor activity.

PLT has not only anticoagulant activity (acquired only after its binding to the thrombin-TM complex and EPCR) but also anti-inflammatory and antiapoptotic properties and is capable of protecting the endothelial barrier function.

The available data on the components of the PC pathway in patients with IBD are controversial. Some authors demonstrated a decrease in PC or PS levels in CD and UC, but other investigators failed to demonstrate any differences. Furthermore, reports have recently been published indicating an increase of PC in IBD.

It was demonstrated in animal models and human tissues that the conversion of PC to APC in inflammatory states is impaired, which may be associated with decreased expression of TM and EPCR on the endothelial cells, as well as with reduced PS levels (the decrease of which in IBD as compared with controls was confirmed in the present study).

Owing to its properties – not only anticoagulant, but also anti-inflammatory, antiapoptotic, and protective for the endothelial barrier function – PC ensures physiological hemostasis, and its administration in some diseases reduces symptoms and mortality rates, which has been demonstrated in humans and animal models. However, the role of PC in IBD still needs to be elucidated.

Our study showed decreased mean levels of PS in both active and nonactive subgroups of IBD compared with the control group. Free PS levels did not correlate with any clinical variables, previous surgery, complications, disease severity or activity. This finding is in line with other publications and may suggest that the persistent activation of coagulation and fibrinolysis may be present in patients in remission. Moreover, clinical data confirms that up to half of the patients with IBD have inactive disease at the time of thrombosis. A decrease in free PS levels may result in a suppressed ability to inhibit blood clot formation because it may hinder inactivation of active factor V and VII by APC.

While analyzing other parameters of the hemostatic system, we demonstrated an increase in fibrinogen and PLT levels and a decrease in APTT in patients with CD and UC compared with controls. Higher fibrinogen levels in acute inflammatory states, coronary artery disease, nephrotic syndrome, and tumors increase the risk of thrombosis.

An increase in CRP levels in IBD and in the active subgroups indicates not only an enhanced inflammatory process, but also increased coagulability in the groups with higher CRP levels. Previous studies demonstrated that CRP not only increases monocyte accumulation and facilitates their reaction with the endothelial cells, but also increases coagulability and thus promotes plasminogen activator inhibitor-1 and tissue factor formation.

Our results regarding the level of PLT in IBD are in line with the previous studies, which showed that PLT levels were elevated in IBD and correlated with disease activity. Moreover, it was shown that PLT in IBD had increased ability to undergo spontaneous aggregation and enhanced sensitivity to various proaggregatory factors. A shortened APTT indicates hypercoagulability but has no diagnostic value.

These changes point to abnormalities in the coagulation system in IBD. Considering the lack of associations between sTM, PC, PS levels and disease activity, it is plausible that multiple factors are implicated in the disturbances of the anticoagulation system.

Our study has several limitations. The size of the study group was too small to draw firm conclusions. Statistical associations reported in our study do not necessarily reflect the cause-effect relationship.
relationships. As it is a hypothesis-generating study, a larger confirmatory study is needed to better understand the role of the coagulation system in IBD.

In conclusion, the results of the present study show that the PC pathway is defective in both CD and UC patients. Our results may confirm the concept that hypercoagulability in IBD is associated not only with the inflammatory process but also with the disturbances in the anticoagulant system, because defective PC pathway was observed both in active and nonactive disease.

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ARTYKUŁ ORYGINALNY

Właściwości przeciwzapalne i przeciwkrzepliwe układu białka C w nieswoistych zapaleniach jelit

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SŁOWA KLUCZOWE
białko C, nieswoiste zapalenia jelit, trombomodulina, zakrzepica, zapalenie

STRESZCZENIE

WPROWADZENIE U pacjentów z nieswoistymi zapaleniemi jelit (NZJ) wykazano zaburzenia między czynnikami prozakrzepowymi, przeciwickrzepowymi oraz fibrynolitycznymi. Układ hemostatyczny jest nieodzownym elementem każdego procesu zapalnego. Niedobory szlaku białka C (protein C – PC) nie tylko sprzyjają zakrzepicy, ale również nasilają proces zapalny.

CELE Celem badania była ocena elementów układu PC i ich korelacja z aktywnością choroby u pacjentów z NZJ.

PACJENCI I METODY Zbadano poziom PC, wolnego białka S (protein S – PS) i rozpuszczalnej trombomoduliny (soluble thrombomodulin – sTM) u 55 kolejnych pacjentów z wrzodziejącym zapaleniem jelita grubeego (WZJG), 50 pacjentów z chorobą Leśniowskiego i Crohna (ChLC) i u 41 zdrowych ochotników. Oceniono korelacje między składowymi układu PC i aktywnością choroby, parametrami hemostazy i markerami procesu zapalnego.

WYNIKI Poziom sTM u chorych z WZJG był wyższy w porównaniu do grupy kontrolnej (24,5 vs 17,5 ng/ml; p = 0,0042). U chorych z NZJ aktywność PC była większa, a aktywność PS była mniejsza w stosunku do grupy kontrolnej (p <0,001). Poziom czynnika martwicy nowotworu α (tumor necrosis factor α – TNF-α) był wyższy u chorych z NZJ, a poziom interleukiny 6 (IL-6) był wyższy jedynie u chorych z ChLC. U chorych z WZJG stwierdzono dodatnią korelację między poziomem sTM oraz poziomem PC i PS (odpowiednio R = 0,28 i R = 0,34; p <0,05). Z aktywnością WZJG korelował jedynie poziom PC (R = 0,3; p <0,05). Nie stwierdzono korelacji między poziomem TNF-α, IL-6, białka C-reactywnego oraz PC, PS i sTM.

WNIOSKI U pacjentów z WZJG i ChLC występują zaburzenia w układzie PC. Nadkrzepliwość w NZJ może być związana nie tylko z procesem zapalnym, ale także z zaburzeniami w układzie antyoksydacyjnym, jako że nieprawidłowość w układzie PC obserwuje się zarówno w aktywnej, jak i nieaktywnej fazie choroby.