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TOPIC HIGHLIGHT

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Inflammatory bowel disease: Epidemiology, pathology and risk factors for hypercoagulability

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Abstract

Hypercoagulability observed in patients with inflammatory bowel diseases (IBD) may lead to thromboembolic events (TE), which affect the venous and arterial systems alike and are an important factor in patients' morbidity and mortality. The risk of TE in IBD patients has been demonstrated to be approximately threefold higher as compared to the general population. The pathogenesis of thrombosis in IBD patients is multifactorial and not fully explained. The most commonly listed factors include genetic and immune abnormalities, disequilibrium between procoagulant and anticoagulant factors, although recently, the role of endothelial damage as an IBD-triggering factor is underlined. Several studies report that the levels of some coagulation enzymes, including fibrinogen, factors Ⅴ, Ⅶ, Ⅷ, active factor Ⅺ, tissue factor, prothrombin fragment 1 + 2 and the thrombin-antithrombin complex, are altered in IBD patients. It has been demonstrated that there is a significant decrease of tissue plasminogen activator level, a marked increase of plasminogen activator inhibitor type 1 and thrombin-activable fibrinolysis inhibitor, a significantly lower level of antithrombin Ⅲ and tissue factor pathway inhibitor. IBD patients have been also observed to produce an increased amount of various anticoagulant antibodies. Hyperhomocysteinemia, which is a potential risk factor for TE was also observed in some IBD patients. Further studies are necessary to assess the role of coagulation abnormalities in IBD etiology and to determine indications for thromboprophylactic treatment in patients at high risk of developing TE.

Key words: Crohn's disease; Hypercoagulation; Risk factors; Thrombosis; Ulcerative colitis

Core tip: Thromboembolic events (TE) in inflammatory bowel diseases (IBD) patients are often overlooked. They affect both the venous and arterial systems. The inflammatory process initiates clotting, impairs the fibrinolytic system and decreases the activity of natural anticoagulation mechanisms. Depression of anticoagulation mechanisms not only increases thrombosis, but also potentiates the inflammatory process. The objective of the present report is to demonstrate the high significance of a problem posed by hypercoagulability in IBD patients based on TE epidemiology, and to present abnormalities in the hemostatic system.

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INTRODUCTION

Inflammatory bowel diseases which include Crohn's disease (CD) and ulcerative colitis (UC), are systemic disorders that predominantly affect the gastrointestinal tract, but are also associated with a number of extraintestestinal manifestations. The majority of extraintestinal complications are characterized by less intense symptoms as compared to those associated with the primary disease, but thromboembolic events (TE) may increase mortality rates in inflammatory bowel diseases (IBD)[1-3]. TE in IBD are often overlooked, since their detection rate in IBD patients is only 6% as compared amounts approximately to 40 % in postmortem examinations[4-6].

The pathogenesis of thrombosis in IBD patients is multifactorial and not fully explained. Numerous investigations have demonstrated qualitative and quantitative abnormalities in procoagulation, anticoagulation and fibrinolytic factors that predispose to thrombosis development in IBD, although some authors have not found any risk factors in about one-half of IBD patients diagnosed with thrombosis.

IBD is a result of an interaction of acquired and genetic factors, with the very inflammatory process being of high significance as well[1,2]. The inflammatory process initiates clotting, impairs the fibrinolytic system and decreases the activity of natural anticoagulation mechanisms; on the other hand, natural anticoagulation factors reduce elevated levels of cytokines triggered by inflammation[7]. Thus, depression of anticoagulation mechanisms not only increases thrombosis, but also potentiates the inflammatory process. An example of the effect of procoagulation factors on the inflammatory process may be found in thrombin, which increases the production of tumor necrosis factor, interleukin (IL)-6 and IL-10 by signaling protease-activated receptors and, therefore, is able to amplify and modify inflammation[8].

The objective of the present report is to demonstrate the high significance of a problem posed by hypercoagulability in IBD patients based on TE epidemiology, and to present abnormalities in the hemostatic system.

EPIDEMIOLOGY OF TE IN IBD PATIENTS

TE are among complications demonstrated in IBD patients, which affect the venous and arterial systems alike and are an important factor in patients' morbidity and mortality. The risk of systemic TE development in IBD patients has been demonstrated to be approximately three-fold higher as compared to the general population[1,2]. TE in IBD has been also demonstrated to develop in younger individuals as compared to the general population[9].

The incidence of TE in IBD has been estimated to be approximatively 0.1%-0.5% per year, with an overall mortality rate as high as 25% per episode[2]. In clinical studies, the incidence rate of TE in IBD patients is estimated as falling in the range of 1.3%-7.7%[1,4,5], although the rate increases to 39%-41% in postmortem examinations[1,6]. For this reason, based on clinical studies published to date, one may say that systemic TE in patients with CD and UC are underdiagnosed.

TE occur mainly during disease exacerbation and are more common in IBD patients with markedly elevated inflammatory markers and presenting with other complications, such as strictures, fistulisation, or abscesses[1,5,10]. The incidence of such episodes is also correlated with the extent of the disease, especially in pancolonic UC patients and in CD patients with colonic involvement[11,12]. However, proctocolectomy is not protective of recurrent deep venous thrombosis (DVT) or pulmonary embolism (PE)[11]. While studying the frequency of TE recurrence in IBD patients in several-year follow-up, an increased risk of venous thromboembolism (VTE) was demonstrated as compared to patients without IBD[1,11,13]. In addition, the risk is three times higher in males as compared to females[13]. In the majority of women, pregnancy is uncomplicated[14]. No higher risk of TE was observed in pregnant women[15].

The age at first VTE is significantly associated with an increased risk of recurrence[13]. The study assessing the risk of TE in the population of Danish children with IBD showed that relative risks were higher in patients under 20 years of age, though actual incidence increased with age[16]. A higher incidence of cerebral TE in pediatric population with IBD was noticed, as well[17].

When compared to general outpatient population, the risk of VTE is 16 times higher in IBD patients who are not hospitalized during the active phase of the disease[18]. However, it is important that thrombosis is also reported in patients with well-controlled disease[5,18]. It has been suggested that in contrast to CD, UC is associated with an increased risk of TE in patients with low-activity disease or even during remission[19,20].

The most common TE in IBD are lower extremity DVT and PE[21]. Occasionally, VTE occur in the cerebral, hepatic, portal, retinal, and mesenteric veins[21-23]. Arterial TE occur less frequently than VTE; the former include thrombosis of the cerebral and retinal arteries and also arteries of upper and lower limbs[23-25]. Moreover, there have been reports of cases of coronary artery thrombosis in young patients with IBD[26].

It is important to remember that in IBD, thrombosis involves not only the systemic veins and arteries, microthrombi may involve the vasculature of the uninflammed intestine as well[27]. For instance, in patients with CD platelet thrombi cross-linked with fibrin were demonstrated in the mucosal microvasculature[28], in patients with UC intracapillary clots have been observed in rectal biopsies[29]. Several observational studies have shown a potential benefit of using heparin treatment in patients with IBD[30,31].

Very interesting results have been presented by Thompson *et al*[32]. The authors have observed that in patients with inherited bleeding disorders such as hemophilia A, hemophilia B and von Willebrand disease, the

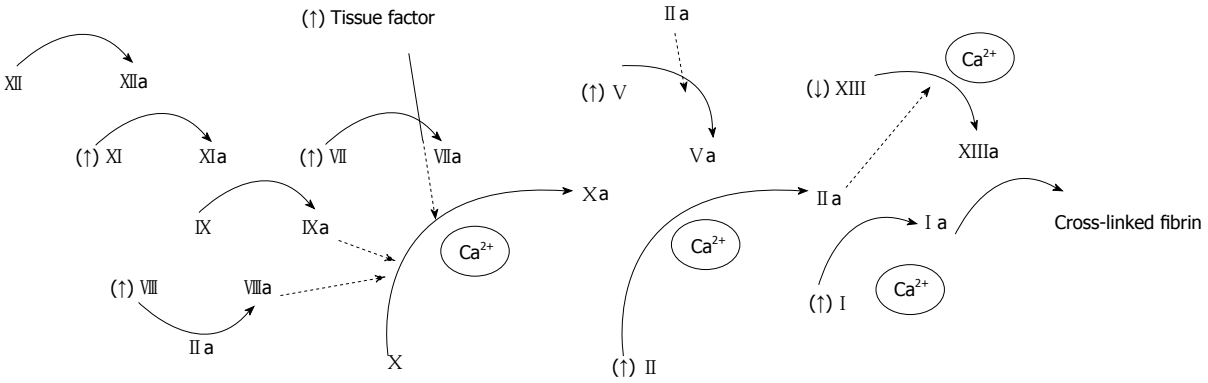

Figure 1 Coagulation cascade model. ↑/↓: Changes in coagulation factors, in patients with inflammatory bowel diseases.

Table 1 Acquired prothrombotic factors in inflammatory bowel diseases

Dehydration
Glucocorticosteroids therapy
Prolonged immobilization
Central venous catheters
Surgical procedures
Oral contraceptives/hormonal replacement therapy
Smoking
Hyperhomocysteinemia

risk of development of either CD or UC was significantly decreased.

It has been suggested that hypercoagulability, prothrombotic state and vascular occlusion play an important role in the pathogenesis of IBD.

ETIOLOGY OF THROMBOSIS IN IBD

IBD patients demonstrate disequilibrium between procoagulant and anticoagulant factors, which predisposes them to develop thrombosis; the abnormalities are both quantitative and qualitative[33].

Acquired factors that affect disturbances in the hemostatic system in IBD include prolonged immobilization, surgical procedures, central venous catheters, glucocorticosteroids therapy, oral contraceptives, hormonal replacement therapy, cigarette smoking, hyperhomocysteinemia, vitamin deficiency, dehydration, as well as damage to the vascular endothelium[21,34,35] (Table 1). Hypercoagulability in both CD and UC may be also triggered by genetic factors[20].

The hemostatic system is an indispensable element of each inflammatory process. During the inflammatory process, not only proteases originating from inflammatory cells are activated, but also those originating from the coagulation and fibrinolysis system[1,36]. For this reason, an increased risk of TE complications is also present during remission period - mostly in patients with UC. The phenomenon is most likely related to the interaction between cytokine mediators of chronic inflammation and the coagulation cascade[34].

The mechanism of an increased thromboembolic risk in IBD is complex, multifactorial and not fully understood. It appears to be multifactorial because no consistent unifying etiology has been identified. However, there are also studies available, where in approximately one-half of IBD patients who developed TE no possible causative factors associated with the complications have been identified[37].

Coagulation cascade

The coagulation cascade is essentially a series of enzymatic conversions, turning inactive proenzymes into activated enzymes and culminating in the formation of thrombin. Thrombin then converts the soluble plasma protein - fibrinogen - precursor into the insoluble fibrous protein - fibrin. Each reaction in the pathway results from the assembly of a complex composed of an enzyme (an activated coagulation factor), a substrate (a proenzyme form of a coagulation factor) and a cofactor (a reaction accelerator).

In the classical cascade model, coagulation has been divided into the extrinsic and intrinsic pathway, converging at the point where factor X (FX) is activated (Figure 1).

Several studies report that the levels of some coagulation enzymes are altered in IBD patients, including increased fibrinogen, increased factor V (FV), Ⅶ (FⅦ) and Ⅷ (FⅧ) and also increased prothrombin fragment 1 + 2 and the thrombin-antithrombin complex[21,34]. The increase in the level of these coagulation factors in CD and UC patients is associated with disease activity[34,38]. Elevated levels of circulating active factor Ⅺ (FⅪ) and tissue factor (TF) have been also reported in IBD[39]. Another abnormality in the coagulation cascade in IBD patients is a decrease in the level of factor XIII (FXIII)[34,40-44]. In the majority of publications a decrease of FXIII level was described in patients with active phase of CD and UC in comparison to non-active phase[34,41,42,44]. There is also a research that does not demonstrate any correlation between disease activity and a FXIII level[40]. One of the potential causes of reduced activated FXIII plasma levels in IBD might be its consumption in the repair of injured tissue[40,41,43] or in the increased formation of microthrombi[42].

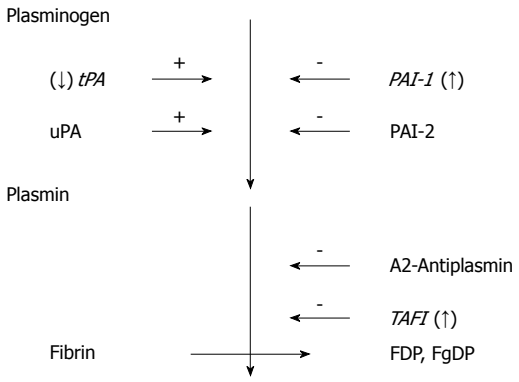

Figure 2 The elements of the fibrinolytic system. tPA: Tissue-type plasminogen activator; uPA: Urokinase plasminogen activator; PAI-1: Plasminogen activator inhibitor type 1; TAFI: Thrombin activatable fibrinolysis inhibitor; FDP: Fibrin degradation products; FgDP: Fibrinogen degradation products. ↑/↓: Changes in coagulation factors, in patients with inflammatory bowel diseases.

Anticoagulation mechanisms

Anticoagulation mechanisms, often referred to by a simplified term "anticoagulation system" are responsible for balancing the procoagulation tendency in the hemostatic system. The system includes the fibrinolysis system, plasma coagulation inhibitors, protein C (PC) anticoagulant system and vascular wall.

Fibrinolysis system

The basic element of the fibrinolysis system is plasminogen, which - following its transformation by activators to an active substance, *i.e.*, plasmin, acts upon fibrinogen, fibrin, FV, FVII, FXIII, von Willebrand factor and platelet glycoproteins.

The elements of the fibrinolysis system - both activators and inhibitors - are presented in Figure 2.

Disturbances in the fibrinolysis system are another very important factor in IBD patients that is associated with hypercoagulability. The fibrynolytic system has been widely investigated in patients with CD and UC, and hypofibrinolysis has been described as a potential contributor to the hypercoagulable state in IBD patients[21,34].

In IBD patients, there has been demonstrated a significant decrease of tissue plasminogen activator (tPA) level, the principal activator of the fibrinolysis system, as compared with the controls[34,45]. With respect to inhibitors of the fibrinolysis system, IBD has been shown to demonstrate a marked increase of plasminogen activator inhibitor 1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI) levels as compared to the healthy control subjects[45,46].

TAFI is a modulator of homeostasis that provides a link between the coagulation system and fibrinolysis system, as well as between the hemostatic system and the inflammatory process[46].

TAFI, a plasma zymogen, can be activated by thrombin, the thrombin-thrombomodulin complex, or plasmin. The activated form of TAFI (TAFIa) removes C-terminal lysine residues from plasmin-modified fibrin which suppresses plasminogen activation, thereby attenuating fibrinolysis. In addition to suppressing fibrinolysis, TAFIa may also be involved in inflammation. Its potential role as a natural anti-inflammatory molecule is currently being explored, with recognition of its ability to inactivate potent anaphylatoxins, C3a and C5a, as well as the proinflammatory mediators, bradykinin and osteopontin[45,46]. TAFI has been also demonstrated to be associated not only with development of thromboembolic complications in various disease entities, but also to affect the course of such diseases[46]. In IBD, a significant correlation has been demonstrated between TAFIa and such inflammatory markers as CRP, fibrinogen, platelets, as well as disease activity[46].

Plasma coagulation inhibitors

Figure 3 presents plasma coagulation inhibitors.

Antithrombin III (ATIII) is the best known natural coagulation inhibitor, its activation is triggered by heparin secreted by mast cells or administered exogenously. ATIII is predominantly synthesized in the liver, vascular endothelial cells, megakaryocytes and platelets. It is the most important endogenous thrombin inhibitor; it forms complex with thrombin in a 1:1 molar ratio, which is subsequently removed from blood by macrophages. ATIII also inactivates factor Xa, factor XIIa, factor XIa and factor IXa. In addition to anticoagulation properties, ATIII has been demonstrated to have anti-inflammatory properties[32]. ATIII decreases expression of CD11b/CD18 cell surface receptors on leukocytes, which decreases leukocyte adhesion, decreases expression of tissue factor and IL-6 in monocytes and endothelium. ATIII also increases prostacyclin formation and decreases nuclear factor (NFκB)[36]. IBD patients have been demonstrated to have a significantly lower levels of ATIII and TF pathway inhibitor (TFPI) as compared to the controls[8,21,34].

TFPI is a protein produced by vascular endothelial cells and megakaryocytes. It is a Kunitz-type protein with three inhibitor domains: the first domain inhibits the factor VIIa/tissue factor complex, the second binds active factor X, the third is responsible for binding TFPI with heparin and lipoproteins[36]. TFPI is a total inhibitor of the TF-dependent coagulation cascade and a marker of endothelial damage[36].

Changes in coagulation and fibrynolytic systems are presented in Table 2.

PC system

The PC system is the most important element of anticoagulation mechanisms. It is presented in Figure 4.

The PC pathway is activated by thrombin bound to endothelial thrombomodulin (TM). Following binding with TM, thrombin acquires abilities to activate PC. PC activation is facilitated when PC is bound to the endothelial cell PC receptor (EPCR). In turn, APC in the presence of protein S (PS) cofactor inactivates active FVIII and FV[7,36]. Additionally, APC has profibrinolytic properties, since it binds PAI-1[7,36].

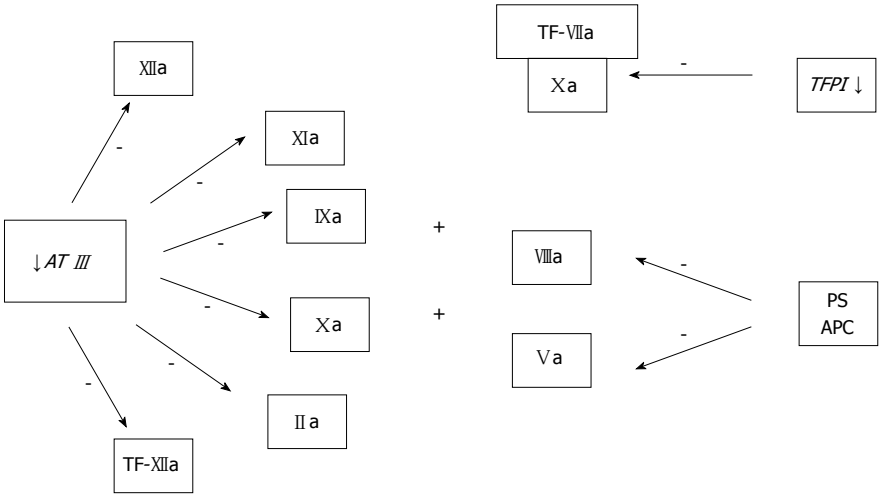

Figure 3 Plasma coagulation inhibitors. AT Ⅲ: Antithrombin Ⅲ; TF: Tissue factor; TFPI: TF pathway inhibitor; PS: Protein S; APC: Activated protein C. ↓: Changes in plasma coagulation inhibitors, in patients with inflammatory bowel diseases.

Table 2 Changes in coagulation and fibrinolytic systems in patients with in inflammatory bowel diseases

Coagulation factors	Fibrinolytic factors	Plasma coagulation inhibitors
Fibrynogen ↑	TAFI ↑	Antithrombin Ⅲ ↓
Factor Ⅴ ↑	PAI-1 ↑	TFPI ↓
Factor Ⅶ ↑	tPA ↓	
Factor Ⅷ ↑		
Factor XI ↑		
Prothrombin fragment 1 + 2 ↑		
Thrombin-antithrombin complex ↑		
TF ↑		
FXIII ↓		

tPA: Tissue plasminogen activator; TAFI: Thrombin-activatable fibrinolysis inhibitor; PAI-1: Plasminogen activator inhibitor 1; TFPI: Tissue factor pathway inhibitor.

Studies have demonstrated that TM as well as APC, in addition to exhibiting anticoagulation properties, also affect the course of the inflammatory process, apoptosis and endothelial barrier[36,47]. Reports of studies on PC, PS and TM levels in patients with CD and UC are contradictory[18,48], although some investigators have demonstrated PC and/or PS deficiency during active IBD phase[21,34].

The available reports regarding plasma TM concentrations in IBD patients have also yielded conflicting results. Several studies have demonstrated that higher TM concentrations occur only in active CD patients as compared to the controls; the above authors have failed to demonstrate any changes in PC and PS levels in IBD. In another study, TM concentrations were higher in UC than in the healthy controls[47].

The controversial character of these findings may result from differences in IBD populations studied (demographic and clinical features, definition of disease activity and evaluation)[47].

It may be also suggested that increased TM or PC levels described by some authors may be associated with their anti-inflammatory properties[47].

Further studies assessing anti-inflammatory properties of TM and PC in IBD are necessary.

Vascular wall

Of importance in regulation of hemostatic mechanisms are subsequent layers of vascular wall: smooth muscles - vasospasm, subendothelial layer - activation of the hemostatic system following endothelial damage, platelet activation, and endothelium.

Hemostatic activity of the endothelium under physiological conditions consists of ensuring non-clotting of blood, non-thrombogenicity of vascular surface, and - after endothelial damage - limiting the thrombus to the thrombogenic site. Endothelial damage disturbs the multifactorial equilibrium provided by endothelial cells, causing development of numerous significant pathological sequelae, such as thrombi formation, hypertension, atherosclerotic lesions, disturbances in tissue perfusion, angiogenesis and inflammatory infiltration[49].

Endothelial damage occurring in numerous diseases is evident though increasing levels of endothelial injury markers. The most frequently used biochemical markers of endothelial damage include von Willebrand factor (vWF), TM, vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1) and endothelin-1 (ET-1).

In recent years, asymmetric dimethylarginine (ADMA) has been also classified as an endothelial damage marker. It is synthesized during the methylation of protein arginine residues by protein arginine methyltransferases and released during proteolysis. ADMA is a major endogenous NO synthase inhibitor and a competitive inhibitor of the cellular L-arginine uptake[50]. Elevation of ADMA induces dysfunction of the endothelium, which becomes clinically evident by impaired endothelium-dependent vasodilation, hyperaggregability of platelets and enhanced monocyte adhesion[50].

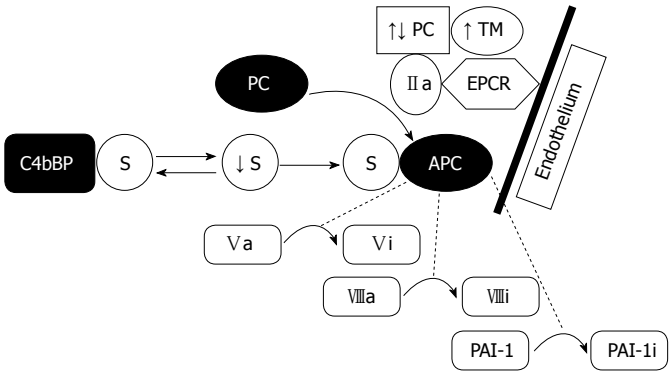

Figure 4 Protein C system. PC: Protein C; APC: Activated protein C; S: Protein S; TM: Thrombomodulin; PAT-1: Plasminogen activator inhibitor 1; EPCR: Endothelial cell PC receptor; C4bBP: C4b-binding protein; Va: V active; Vi: V inactive; VIIIa: VIII active; VIIIi: VIII inactive. ↑/↓: Changes in protein C system, in patients with inflammatory bowel diseases.

According to the published studies, there has been observed an increase of such endothelial damage markers as vWF, TM, endothelial PC receptor (EPCR) and ADMA in IBD patients; they have been also found to correlate with disease activity and inflammatory markers[34,46,47,50].

Vascular endothelial damage is believed to be a factor that increases the risk of TE in IBD.

Homocysteine

Homocysteine is an amino acid formed from S-adenosylomethionine (SAM), in all types of cells in the human body. It participates in metabolism of numerous compounds that are indispensable for the organism to function.

Homocysteine is a pro-coagulation factor, since it evokes changes in vascular walls and triggers increased expression of TF and FV, decreased expression of TM and tPA and decreased activation of PC. Elevated plasma homocysteine levels facilitate development of both arterial and venous thrombosis[34]. Recently, homocysteine has been also shown to participate in microvascular inflammation in IBD, triggering endothelial inflammation, resulting in VCAM-1 upregulation, monocyte chemoattractant protein-1 (MCP-1) production and p38 phosphorylation. Such changes lead to increased adhesion of T cells and monocytes to the endothelium[51].

Hyperhomocysteinemia is a potential risk factor for TE in IBD patients and can be secondary to folic acid and vitamin B12 deficiencies, medications (methotrexate, sulphalazine, glucocorticosteroids), smoking and nutritional deficiencies[21,34].

Both plasma and mucosal homocysteine levels have been demonstrated to be significantly higher in IBD patients as compared to the healthy controls and correlated with disease activity[51,52]. However, there is no evidence that an increase in homocysteine level is of greater proportion in IBD patients with TE *vs* those without. The risk assessment of hyperhomocysteinemia-related thrombosis in IBD requires further investigation[52].

Platelets in IBD

Blood platelet levels may be considerably increased in active IBD both in CD and UC patients; this is a reaction to an intensified inflammatory process. Regardless of inflammatory process exacerbation, approximately 30%-50% of IBD patients develop spontaneous platelet aggregation or platelet hypersensitivity to low concentrations of aggregating agents[53]. The final stage of platelet hyperactivation has been found to be mediated by the CD40-CD40 ligand (CD40L) pathway. The surface CD40L is an activation marker that allows platelets to interact with a broad variety of immune and non-immune cells. It has been demonstrated that in IBD patients platelets overexpress CD40L protein up to four times more frequently than platelets from control subjects, and release more soluble CD40L (sCD40L) to the plasma, leading to a 15 fold increase in CD40L plasma levels. In general elevated levels of sCD40L are associated with an increased risk of TE development which is also true for patients with IBD[53]. It has been observed that an increased platelet activity in IBD is also dependent on increased expression of surface activation markers, such as P-selectin and GP53 and on serum levels of platelet activation marker β-thromboglobulin[34,54]. The higher platelet activity state mentioned above has been noted to be independent of clinical activity of the disease; the chronic disease process has been suggested to lead to increased platelet activity even in remission state[34,54].

Finally, platelets are involved in chronic intestinal inflammation, what has been demonstrated in studies evaluating anus sections collected from IBD patients. Mucosal intravascular microthrombi have been shown both in CD and UC patients[29,53]. In addition, the investigators have found that platelets of patients with IBD express high levels of surface CD40L, creating a physical and biological bridge that allows interaction with human intestinal microvascular endothelial cells causing their activation[34,54], what leads to up-regulation of VCAM-1 and ICAM-1 by activated platelets through the CD40-dependent pathway and to increased production of IL-8 by endothelial cells, also through this pathway, and an increase in T cell adhesion to the endothelium[34].

Autoantibodies

IBD patients have been observed to produce increased amounts of various antibodies; some of them are anticoagulant antibodies and thus may increase the risk of thrombosis.

Antiphospholipid antibodies include anticardiolipin (aCL) antibodies and lupus anticoagulants (LAC). The antibodies may increase the risk of thrombosis through ac-

tivation of platelets and endothelial cells and by decreasing anticoagulant activity of proteins. In IBD patients as compared to the controls, the level of aCL antibodies is approximately 20%-30% higher, while the level of LAC antibodies is approximately 19% higher[55,56].

In IBD, the prevalence of antibodies against β2-glucoprotein I (β2-GPI), the cofactor that mediates binding of aCL antibodies to cardiolipin, is higher than in the controls, with an average incidence of 9%[56].

Antibodies against PS have been described in patients with IBD. The antibodies could reduce the natural anticoagulant potential[48]. However, in up-to-date publications there is no good evidence that these antibodies play any role in thrombotic risk[48].

Nevertheless, no significant differences have been demonstrated in the prevalence of the above antibodies in IBD patients with diagnosed TE as opposed to the IBD group without such complications[48,56]. Further observations and studies are necessary to allow for a possible confirmation of the role of these antibodies in the development of TE.

Genetic factors

Genetic factors that have been implicated to play role in TE in IBD include FV Leiden (FVL, G1691A), the genetic variation of the prothrombin gene mutation (*G20210A*), methylenetetrahydrofolate reductase gene mutation (MTHFR, C677T), plasminogen activator inhibitor type 1 (*PAI-1*) gene mutation and FXIII (val-34leu)[20,34,57-59].

FVL is an arginine to glutamine missense mutation in the *FV* gene at position 506. FVL is the most frequent cause of inherited thrombophilia, it renders the activated FV form relatively resistant to degradation by activated protein C (APC), resulting in higher thrombin generation. The prevalence of FVL ranges from 20% to 30% in unselected patients with venous thrombosis[20]. Most of studies have shown no difference in the prevalence of FVL between IBD patients and the healthy controls[20,34], but in IBD patients with TE, the prevalence of FVL was significantly higher than in IBD patients without TE[20]. Additionally, the prevalence of FVL in IBD patients with TE is comparable to its prevalence in non-IBD patients with TE[58,60]. Although somewhat conflicting, these genetic studies suggest that FVL as a risk factor for TE in IBD patients matches that of the general population.

The *G20210A* gene mutation is the second most frequent genetic prothrombic mutation after FVL. The prevalence of *G20210A* mutation is about 2% in healthy controls and 6.2% in patients with thrombosis[60]. However, several studies have demonstrated the same prevalence of the gene mutation in IBD patients with and without TE[60,61]. Some investigators have shown a close association between IBD and the presence of the *G20210A* mutation[56,57].

Methylenetetrahydrofolate reductase (MTHFR) is a critical enzyme involved in the remethylation pathway of homocysteine metabolism. A common mutation (C677T) has been identified in the *MTHFR* gene. The homozygous carries of this polymorphism are found in around 10% of the population and the polymorphism may be a cause of moderate hyperhomocysteinemia. Some studies have demonstrated a weak association between C6777T homozygosity in the population and the risk of thrombosis[62]. However, the study that associated the prevalence of C677T homozygosity between IBD thrombotic and IBD non-thrombotic subjects has shown no significant differences[58,60].

The *FXIII* gene mutation (val34leu) is associated with a higher FXIII activation rate and leads to a 20%-40% risk reduction of venous thrombosis for homozygous carries, which are found in around 10% of the population[63]. The FXIII mutation has been evaluated in IBD patients, but the available studies have not demonstrated any significant differences in the prevalence of this polymorphism in IBD patients with respect to the general population[58,64].

PAI-1 gene mutation - the 4G/4G genotype - is associated with an overexpression of *PAI-1*, which may cause a decreased fibrinolysis. The 4G/4G genotype has been demonstrated to be a risk factor in myocardial infarction, arterial thrombosis and DVT[20,65]. The available studies have demonstrated a higher prevalence of the genotype in IBD patients as compared to the general population[65].

Investigations performed in IBD patients also assess other genetic hypercoagulability factors, such as deficiency of PC and PS, and ATⅢ mutation[20].

Finally, in spite of numerous genetic studies performed in IBD, no unambiguous association has been demonstrated between genetic factors and causes of hypercoagulability in both CD and UC[20,34].

Medications

Some medications used in the treatment of IBD patients may affect haemostatic system. 5-ASA used in a combination with oral anticoagulants might increase the risk of bleeding. Carty *et al*[66] observed that 5-ASA given orally or in vitro inhibits platelet activation.

It has been confirmed by many studies that glucocorticoids increase the risk of VTE[67]. Johannesdottir *et al*[67] in a population-based case-controlled study observed a higher risk of VTE among present, new, continuing and recent glucocorticoids users but not among former ones. Glucocorticoids also inhibit oral anticoagulants.

Data regarding coagulation and use of anti TNF antagonists are conflicting. For instance, in a national prospective observational cohort study in Great Britain use of anti-TNF therapy was not associated with an increased risk of VTE in rheumatoid arthritis patients[68]. However, the majority of publications confirm such a relationship[69]. TEs have been noted in about 4.5% of patients treated with TNF antagonists. One of the possible explanations includes involvement of anti-drug antibodies that might be found in some patients. It has been speculated that antigen-Ab complexes could trigger thrombosis by activating either platelets or the comple-

ment system[69]. Another hypothesis is based on predisposition of some patients to lupus-like reactions, including antiphospholipid syndrome[69]. The inhibition of TNF leads to overproduction of interferon-α what might facilitate the development of lupus-like syndrome.

Concomitant use of thiopurines and anticoagulants may foster decrease in the effect of warfarin, what might be caused by reduced bioavailability, enhanced warfarin metabolism, or increased prothrombin activity[70].

A meta-analysis of eight randomized-controlled trials performed in 2007 demonstrated that administration of heparin in patients with UC is safe, but does not give any benefit over conventional therapy[71]. In 2010, a review of randomized trials confirmed no benefit of low molecular weight heparins (LMWH) administered subcutaneously over placebo for clinical remission induction in patients with UC. However, high dose LMWH administered *via* an extended colon-release tablet showed benefit over placebo for clinical remission and endoscopic improvement. There is no evidence to support the use of unfractionated heparin for the treatment of active UC[72].

Thromboprophylaxis

There are no unambiguous indications to use thromboprophylaxis in patients with IBD[73]. Many national guidelines support their use in this patient population[74]. European Crohn's and Colitis Organisation (ECCO) suggests to consider prevention with both mechanical thromboprophylaxis and heparin in patients with UC at risk of TE and antithrombotic prophylaxis in all hospitalized patients with CD, especially in the event of prolonged immobilization[75-78]. Evidence from randomized trials confirms that use of heparin and LMWH is generally safe in patients with IBD[74]. Patients with IBD should be also informed about thrombotic risk factors such as oral contraceptive use and long-distance travel[77,78].

CONCLUSION

Despite numerous studies, to date, the pathogenesis of IBD has not been unambiguously determined. The most commonly listed factors include genetic and immune abnormalities, although recently, discussions focus on the role of endothelial damage and coagulation disturbances as IBD-triggering factors. Persistent hypercoagulation may influence the clinical course of IBD and most likely is related to the interaction between chronic inflammatory process and coagulation cascade[34]. Activation of coagulation acts as an element of the inflammatory response by directly mediating cytokine responses. Also hypofibrinolysis seems to be a typical feature of inflammation[34]. That is why, the majority of TEs occur during the active phase of IBD[77,78]. Acquired prothrombotic factors also play a crucial role in development of TE in IBD patients.

Further studies are necessary to assess the role of coagulation abnormalities in IBD etiology and to determine indications for thromboprophylactic treatment in patients at high risk of developing TE.

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