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TOPIC HIGHLIGHT

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Venous thrombosis and prothrombotic factors in inflammatory bowel disease

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Abstract

Patients with inflammatory bowel disease (IBD) may have an increased risk of venous thrombosis (VTE). PubMed, ISI Web of Knowledge and Scopus were searched to identify studies investigating the risk of VTE and the prevalence of acquired and genetic VTE risk factors and prothrombotic abnormalities in IBD. Overall, IBD patients have a two- to fourfold increased risk of VTE compared with healthy controls, with an overall incidence rate of 1%-8%. The majority of studies did not show significant differences in the risk of VTE between Crohn's disease and ulcerative colitis. Several acquired factors are responsible for the increased risk of VTE in IBD: inflammatory activity, hospitalisation, surgery, pregnancy, disease phenotype (*e.g.*, fistulising disease, colonic involvement and extensive involvement) and drug therapy (mainly steroids). There is also convincing evidence from basic science and from clinical and epidemiological studies that IBD is associated with several prothrombotic abnormalities, including initiation of the coagulation system, downregulation of natural anticoagulant mechanisms, impairment of fibrinolysis, increased platelet count and reactivity and dysfunction of the endothelium. Classical genetic alterations are not generally found more often in IBD patients than in non-IBD patients, suggesting that genetics does not explain the greater risk of VTE in these patients. IBD VTE may have clinical specificities, namely an earlier first episode of VTE in life, high recurrence rate, decreased efficacy of some drugs in preventing further episodes and poor prognosis. Clinicians should be aware of these risks, and adequate prophylactic actions should be taken in patients who have disease activity, are hospitalised, are submitted to surgery or are undergoing treatment.

Key words: Acquired; Genetic; Prothrombotic; Venous thrombosis; Risk of venous thrombosis; Inflammatory bowel disease

Core tip: In inflammatory bowel disease (IBD), there is an increased risk of venous thrombosis (VTE) due to inflammatory activity, hospitalisation, surgery, pregnancy, disease phenotype and drug therapy. Classical genetic alterations are not generally found more often in IBD patients than in non-IBD patients, suggesting that genetics does not explain the greater risk of VTE in these patients. IBD VTE may have clinical specificities, namely an earlier first episode of VTE in life, high recurrence rate, decreased efficacy of some drugs in preventing further episodes and poor prognosis.

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INTRODUCTION

The possible association between inflammatory bowel disease (IBD) and venous thrombosis (VTE) was first reported in 1936 by Bargen *et al*[1], who described 18 patients with thromboembolic disease (predominantly venous) from among more than 1000 patients treated for IBD at the Mayo Clinic. Since that time, several publications have suggested that patients with IBD have an increased risk of VTE, including deep venous thrombosis (DVT), pulmonary emboli, portal vein thrombosis, cerebral venous sinus thrombosis, Budd Chiari syndrome and retinal vein thrombosis[2-5]. The overall incidence rate of VTE in IBD patients has been estimated to be 1%-8%, although necropsy studies report an incidence of 39%-41%[2-5]. One systematic review[4] and one meta-analysis[3] showed a higher VTE risk in IBD patients, even after correction for known prothrombotic factors such as smoking and obesity[3]. Nevertheless, other studies, such as that of Grip *et al*[6], show a similar risk between IBD and the background population. However, in that report, where the incidence of VTE in the IBD cohort (0.15% per year) was comparable with that of the background population, the differences in age between the groups could have affected the conclusions[6].

It is important to stress that most of the evaluated studies were retrospective. When the IBD population was compared with other patients or healthy controls, most of the classical prothrombotic risks were not assessed, and therefore a bias could have been present. Therefore, the aim of this review was to assess the risk of VTE and the prevalence of acquired and genetic VTE risk factors and prothrombotic abnormalities in IBD.

SEARCH STRATEGY

A systematic review was conducted on published articles that assessed the risk of VTE and the prevalence of acquired and genetic VTE risk factors and prothrombotic abnormalities in IBD through a literature search of PubMed, ISI Web of Knowledge and Scopus. This search was performed in September 2013 using the following medical terms: "venous thrombosis IBD", "acquired venous thrombosis risk factor IBD", "genetic venous thrombosis risk factor IBD", "coagulation IBD", "fibrinolysis IBD", "platelets IBD" and "endothelium IBD". Additionally, a comprehensive search of reference lists of all review articles and original papers achieved by this method was performed to identify additional reports that could be included in the final analysis. Potential studies were initially screened by title and abstract. Potential exclusion criteria to reduce the risk of bias and unnecessary observations included case reports on single patients, book chapters and studies exclusively on arterial thrombosis. A total of 207 articles were studied to construct this review.

RISK OF VTE IN IBD

A summary of the controlled studies comparing the risk of VTE in IBD patients with the risk of VTE in non-IBD patients is presented in Table 1.

General risk

In one of the earliest studies evaluating the incidence of VTE in IBD patients, 61 out of 7199 patients (0.84%) developed VTE during an 11-year period from January 1970 to December 1980 at the Mayo Clinic, with similar rates of VTE observed in patients with Crohn's disease (CD) and ulcerative colitis (UC)[7]. In 2001, Bernstein *et al*[8] published the first study on the risk of VTE in IBD in a large population-based study using health administrative data from the province of Manitoba, Canada, in which they applied validated case ascertainment definitions of CD and UC (Table 1). The incidence rate for VTE in IBD patients was 45.6 per 10000 persons-year of follow-up, and IBD patients were 3.5 times more likely to develop VTE than the controls. Similar rates of VTE were observed in CD and UC and in males and females. The highest rates of VTE were observed among patients over 60 years old; however, the highest incidence rate ratio (IRR) for VTE was among patients younger than 40 years old (IRR = 6.02, 95%CI: 3.92-9.12). In 2004, Miehsler *et al*[9] compared the risk of VTE in patients with IBD and other chronic inflammatory diseases (rheumatoid arthritis and coeliac disease) with matched controls (Table 1). The subjects with IBD had a significantly higher risk of VTE compared with the matched controls [prevalence: 6.15% *vs* 1.62%; odds ratio (OR) = 3.6, 95%CI: 1.7-7.8], whereas the subjects with rheumatoid arthritis or coeliac disease had a risk of VTE similar to that of the controls. In 2007, the risk of VTE among 17 chronic illnesses was evaluated (Table 1)[10]. The relative risk (RR) of VTE was nearly twofold higher in IBD patients than in the matched controls (OR = 1.84, 95%CI: 1.29-2.63), with only cancer and heart failure carrying a greater risk of VTE than IBD.

IBD, activity, hospitalisation and surgery

Some studies have shown that the risk of VTE may be higher in UC than in CD [11,12], with other showing the opposite[13]; however, the majority of did not show significant differences in the risk of VTE between CD and UC[3,4,8,14,15]. A recent meta-analysis showed similar risks in patients with UC (RR = 2.57, 95%CI: 2.02-3.28; n = 6 studies) and CD (RR = 2.12, 95%CI: 1.40-3.20; n = 5 studies)[3].

Several studies reported IBD activity in 45% to 90% of patients at the time of VTE diagnosis[8,9,16-18]. The asso-

Table 1 Risk of venous thrombosis in inflammatory bowel disease patients relative to non-inflammatory bowel disease patients

Ref.	Design	Population		Risk measure (95%CI)	Controlled variables
		IBD	Controls		
Grip *et al*[6], 2000 Sweden	Retrospective cohort study Inpatients Records from 2 university hospitals	1253 patients	387 (significant age differences between the IBD cohort and controls)	Incidence rate of VTE 1.5/1000 IBD per year (comparable to the background population)	
Bernstein *et al*[8], 2001 Canada	Retrospective cohort study Inpatients Manitoba Health administrative 1984-1997	5529 patients	Approximately 55000 year, age, gender and postal area of residence matched members of the general population	DVT RR 4.7 (3.5-6.3) CD RR 2.8 (2.1-3.7) UC PE RR 2.9 (1.8-4.7) CD RR 3.6 (2.5-5.2) UC	
Miehsler *et al*[9], 2004 Austria	Retrospective cohort study Outpatients and inpatients Three outpatient clinics of Division of Gastroenterology and Hepatology	618 patients	707 age and gender matched controls	Incidence rate of VTE 6.2% IBD 1.6% Controls VTE aOR 3.6 (1.7-7.8) IBD	Operation, injuries, oral contraceptive use, pregnancy, body mass index and smoking
Bernstein *et al*[20], 2007 Canada	Retrospective cohort study Inpatients The Statistics Canada's Health Person Oriented Information database 1994-2004	About 22000 to 25000 patients	About 2.5 to 3.2 million age and gender matched controls	VTE ⩾ 50 yr old RR 1.3 (1.23-1.37) IBD < 50 yr old RR 1.57 (1.42-1.72) IBD	
Huerta *et al*[10], 2007 United Kingdom	Prospective cohort study with nested case-control analysis Outpatients and inpatients General Practice Research Database - GPRD 1994-2000	6550 patients	10000 age, gender and year matched controls	VTE OR 1.84 (1.29-2.63) IBD	
Nguyen *et al*[12], 2008 United States	Retrospective cohort study Inpatients Nationwide Inpatient Sample 1998-2004	116842 patients (73197 CD and 43645 UC patients)	522703 controls	VTE aOR 1.48 (1.35-1.62) DC aOR 1.85 (1.70-2.01) UC	Age, gender, calendar year, health insurance payer, comorbidity, presence of IBD related surgery, geographic location, and hospital characteristics
Ha *et al*[148], 2009 United States	Retrospective cohort study Outpatients and inpatients MarketScan Commercial Claims and Encounters database - Thomson Reuters 2001-2006	17487 patients (7480 CD and 9 968 UC patients)	69948 age, gender and index date matched controls	PVT aHR 6.2 ($P < 0.05$) IBD DVT aHR 2.3 ($P < 0.0001$) IBD PE aHR 1.7 ($P < 0.001$) IBD	Hypertension, diabetes, hyperlipidemia, and, in women, the use of contraceptives
Nguyen *et al*[14], 2009 United States	Retrospective cohort study Pregnant hospitalized women Nationwide Inpatient Sample 2005	3740 patients (2372 CD and 1368 UC patients)	4.21 million pregnant women	VTE aOR 6.12 (2.91-12.9) CD aOR 8.44 (3.71-19.2) UC	Maternal age, race/ethnicity, median neighbourhood income, comorbidity, health insurance, geographical region, hospital location and teaching status and caesarean delivery
Grainge *et al*[19], 2010 United Kingdom	Retrospective cohort study Outpatients and inpatients General Practice Research Database 1987-2001	13 756 patients (4835 CD and 6765 UC patients)	71672 age, gender, and general practice matched controls	VTE aHR 3.4 (2.7-4.3) IBD	Age, sex, body-mass index, smoking, cancer diagnosis and history of pulmonary embolism or deep vein thrombosis
Novacek *et al*[16], 2010 Austria	Retrospective cohort study Outpatients IBD patients from 14 Austrian centers specializing in the treatment of patients with IBD (2006-2008) and controls patients from 4 centers in Austria (1992-2008) 2006-2008	86 patients with history of unprovoked VTE	1255 controls with unprovoked VTE	Recurrence 5 yr after discontinuation of anticoagulation therapy aRR 2.5 (1.4-4.2) IBD	Age, gender, factor V Leiden, prothrombin G20210A mutation, high factor VIII (> 234 IU/dL), duration of anticoagulation and body mass index

Scarpa *et al*[147], 2010 Italy	Prospective case-control study Hospitalized patients who had major colo-rectal surgery Patients admitted for colorectal surgery in the institute of Clinica Chirurgica I of the University of Padova (Italy) 2004-2006	323 patients	432 controls	Incidence rate of VTE in surgical IBD patients *vs* surgical non IBD patients (both with prophylactic therapy) 1.9% *vs* 0% VTE with prophylactic therapy OR 5.9 (0.9-39.7) UC	
Kappelman *et al*[13], 2011 Denmark	Retrospective cohort study and nested case-control study Danish National Patient Registry 1980-2007	49799 patients (14211 CD and 35 229 UC patients)	477504 age and gender matched members of the general population	All VTE HR 2.0 (1.8-2.1) IBD HR 2.2 (2.0-2.5) CD HR 1.9 (1.8-2.0) UC Unprovoked VTE HR 1.6 (1.5-1.8) IBD HR 2.0 (1.6-2.5) CD	Comorbidities and medications
Merrill *et al*[23], 2011 United States	Retrospective cohort study Surgical patients National Surgical Quality Improvement Program 2008	2249 patients	269119 patients without IBD who were hospitalized and underwent surgery	HR 1.5 (1.4-1.7) UC aOR 1.7 (1.3-2.2) IBD VTE aOR 2.03 (1.52-2.70) IBD	Age, gender, race/ethnicity, admitted from home, smoker, BMI > 30, medical history, clinical factor
Rothberg *et al*[22], 2011 United States	Retrospective cohort study Inpatients 374 US hospitals 2004-2005	814 patients	241924 controls	VTE aOR 3.11 (1.59-6.08) IBD	Age, gender, VTE prophylaxis, length of stay ⩾ 6 d, primary diagnosis, comorbidities, cancer and treatments
Saleh *et al*[11], 2011 United States	Retrospective cohort study Inpatients National Hospital Discharge Survey 1979-2005	2932000 patients (1803000 CD and 1129000 UC patients)	918570000 age, gender matched controls	VTE HR 1.08 (1.06-1.09) CD HR 1.64 (1.62-1.66) UC	
Sridhar *et al*[21], 2011 United States	Cross-sectional study Inpatients Nationwide Inpatient Sample 2010	148229 patients	17261952 controls	VTE (DVT, PE and/or PVT) aOR 1.38 (1.25-1.53) IBD	Hypertension, diabetes mellitus and hyperlipidemia
Bröms *et al*[15], 2012 Sweden	Retrospective cohort study Pregnant women Medical, Patient, and Prescribed Drug Registers of all residents in Sweden 2006-2009	1996 patients (787 CD and 1209 UC patients) who gave birth to a single infant	10773 women without IBD who gave birth to a single infant	VTE aRR 2.65 (0.65-10.1) CD (with inactive disease) aRR 3.78 (1.52-9.38) UC	Age, parity, smoking, body mass index and comorbidities

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; VTE: Venous thrombosis; DVT: Deep venous thrombosis; PE: Pulmonary emboli; PVT: Portal vein thrombosis; aRR: Adjusted relative risk; aOR: Adjusted odds ratio; aHR: Adjusted hazard ratio.

ciation of VTE and IBD flares was assessed using a large primary care database from the United Kingdom (Table 1)[19]. According to the data from this assessment, the risk of VTE was increased most prominently during a flare of IBD [hazard risk (HR) = 8.4, 95%CI: 5.5-12.8], compared with periods of chronic activity (HR = 6.5, 95%CI: 4.6-9.2) and periods of clinical remission (HR = 2.1, 95%CI: 1.6-2.9). The RR at the time of a flare, compared with a matched control, was higher during non-hospitalised periods (HR = 15.8, 95%CI: 9.8-25.5 *vs* HR = 3.2, 95%CI: 1.7-6.3). However, this finding must be interpreted with caution because the lower RR during hospitalised periods is related to a higher absolute risk (37.5 *vs* 6.4 per 1000 persons-years), and the treatment with corticosteroids in patients with active disease may also be an additional risk factor for the development of VTE. Moreover, the use of VTE prophylaxis in hospitalised patients can also contribute to a lower RR of VTE during hospitalisation. Bernstein *et al*[20] showed higher VTE rates in hospitalised IBD patients than in non-IBD hospitalised patients regardless of age (Table 1). IBD patients who were younger than 50 years had a higher RR than those who were older than 50 years (RR = 1.57, 95%CI: 1.42-1.72 *vs* RR = 1.30, 95%CI: 1.23-1.37)[20]. Nguyen *et al*[12] compared the risk of VTE between hospitalised IBD patients and randomly selected hospitalised non-IBD patients (Table 1) and reported that IBD patients had an adjusted 1.7-fold [adjusted OR (aOR) = 1.66, 95%CI: 1.33-2.06] increased rate of VTE compared with non-IBD patients. In 2011, three studies were published showing a 1.1- to 3.1-fold higher risk of VTE in hospitalised IBD patients (Table 1)[11,21,22].

The risk of VTE in IBD was also evaluated in the surgical setting. Merrill *et al*[23] compared the risk of VTE between patients with IBD and patients without IBD who underwent surgery in 211 hospitals participating in the American College of Surgeons National Surgical Quality Improvement Program (Table 1). The incidence of VTE was 2.5% in IBD patients (n = 57) *vs* 1.0% (n = 2608)

Table 2 Prothrombotic risk factors and abnormalities associated with inflammatory bowel disease

Acquired prothrombotic risk factors
Infection or inflammation, previous thromboembolism, age, smoking, malignancy, central venous catheter, surgery, trauma, immobilization, Pregnancy, drugs (oral contraceptives, steroids), antiphospholipid antibody syndrome, hyperhomocysteinemia, fluid depletion
Genetic prothrombotic risk factors
Factor V Leiden, prothrombin mutation, deficiency of protein C, deficiency of protein S, deficiency of antithrombin, PAI-1 mutation, factor XII mutation and MTHFR mutation
Abnormalities of coagulation
↑ TF, factors VII, FXII, FXI, FX and FV, prothrombin and fibrinogen
↓ AT, protein C, protein S, EPCR, TM and TFPI
↑ Prothrombin fragment 1+2, TAT complexes, fibrinopeptide A and fibrinopeptide B
↓ Factor XIII
Abnormalities of fibrinolysis
↓ t-PA
↑ PAI-1 and TAFI
↑ D-dimer
Abnormalities of platelets
↑ Number, activation (CD40L and P-selectin) and aggregation
Abnormalities of endothelium
↓ NO
↑ vWF

PAI-1: Plasminogen activator inhibitor 1; MTHFR: Methylenetetrahydrofolate reductase; TF: Tissue factor; AT: Antithrombin; EPCR: Endothelial cell protein C receptor; TM: Thrombomodulin; TFPI: Tissue factor-pathway inhibitor; TAT: Thrombin-antithrombin; t-PA: Tissue plasminogen activator; TAFI: Thrombin-activatable fibrinolysis inhibitor; CD40L: CD40 ligand; vWF: von Willebrand factor.

in the controls. IBD remained a significant predictor of VTE after multivariate adjustment (OR = 2.03, 95%CI: 1.52-2.70). Another interesting finding of this was the observation that the risk persisted even when procedures on small and large bowels were excluded, with IBD patients undergoing non-intestinal procedures having a 4.45-fold increased risk of VTE compared with non-IBD patients. Furthermore, in a large cohort of surgical IBD patients, bleeding disorders, steroid use, anaesthesia time, emergency surgery, haematocrit < 37%, malnutrition and functional status were identified as potentially modifiable risk factors for postoperative VTE in IBD patients[24].

Pregnancy

The risk of VTE in IBD was also evaluated during pregnancy and puerperium. According to the Nguyen *et al*[14] study, based on nationwide inpatient sample data (database containing discharge abstracts from 1054 hospitals in the United States), the aOR of VTE was substantially higher in women with CD (aOR = 6.12, 95%CI: 2.91-12.9) and UC (aOR = 8.44, 95%CI: 3.71-19.2) compared with the non-IBD obstetric population, and this increased risk was independent of whether the women underwent a caesarean section (Table 1). A similar study conducted by Bröms *et al*[15] in Sweden also showed an increased risk of VTE in pregnant IBD patients compared with non-IBD pregnant patients but showed a lower odds ratio (aOR = 2.65, 95%CI: 0.65-10.1 for CD; aOR = 3.78, 95%CI: 1.52-9.38 for UC) (Table 1). For women with UC, the increased risk of VTE seemed to be highest during pregnancy and not during puerperium like in the general population of women giving birth.

IBD-phenotype risk factors

Several IBD-phenotype risk factors have been shown to affect the risk of VTE. Nguyen *et al*[12] reported that fistulising disease was independently associated with a greater VTE risk (OR = 1.39, 95%CI: 1.13-1.70). Colonic involvement in CD patients or extensive disease in UC patients was also associated with an increased VTE risk. A study by Solem *et al*[17] showed that CD patients with VTE typically had colonic disease involvement (ileocolonic in 56% and colonic in 23%), and most UC patients with VTE (76%) had pancolonic disease. Nguyen *et al*[12] found a higher risk of VTE in CD patients with colonic-only disease that was 40% higher than the risk of VTE in those with small bowel-only disease. In UC patients, 25% experienced VTE after proctocolectomy, and VTE recurrence rates were not improved by proctocolectomy[17].

IBD-nonspecific acquired risk factors

In IBD, several nonspecific acquired risk factors, other than those previously discussed, often increase the risk of VTE, such as oral contraceptive/hormone substitution use, smoking and drug therapy (Table 2). In most studies, at least one of the known clinical risk factors for VTE was present in approximately 20%-50% of IBD patients with VTE at the time a TE occurred[9,16,18,25]. Approximately 30% of these patients may have two or more risk factors[9].

PROTHROMBOTIC ABNORMALITIES IN IBD

Impact of inflammation on coagulation

Although the causes of the increased risk of VTE in IBD are not yet completely understood, most studies suggest that this risk is largely dependent on the biological and biochemical effects exerted by the activation of the inflammatory pathways (*e.g.*, cells and cytokines) in

the haemostatic system. In fact, there is now convincing evidence from clinical, epidemiological and experimental studies that inflammation and VTE are related[5,26-28]. Many inflammatory diseases other than IBD, such as systemic lupus erythematosus, Behçet's disease, polyarteritis nodosa and polymyositis/dermatomyositis, have been associated with an increased risk of VTE in several clinical and epidemiological studies[5,26-28]. This association appears to be the strongest when the time between the exposure and the outcome is short, *e.g.*, when the inflammatory disease was experienced recently or, more specifically, in the active stage of an inflammatory disease (flare-up)[5,26-28]. In many inflammatory diseases, such as systemic lupus erythematosus and Behçet's disease, VTE may be part of the presentation of those diseases. VTE in IBD may complicate the differential diagnosis with other inflammatory diseases that may also lead to VTE and intestinal inflammation, such as Behçet's disease.

The impact of inflammation on coagulation has been confirmed by several experimental studies showing that inflammatory mechanisms shift the haemostatic balance to favour the activation of coagulation and, in the extremes, VTE[27].

Tumour necrosis factor-alpha (TNF-α) and CD40 ligand (CD40L), two inflammatory cytokines, and C-reactive protein (CRP), a liver-synthesised acute phase protein, have been shown to induce the expression of tissue factor (TF) on the cell surface of leucocytes[29-31]. Interleukin (IL)-6, an inflammatory cytokine, and TNF-α have been shown to lead to thrombin generation[32,33]. Of the natural anticoagulant pathways, the protein C pathway and heparin-antithrombin pathway have been shown to be downregulated by IL-1β and TNF-α[34,35], whereas the tissue factor pathway inhibitor (TFPI) has been shown to be inhibited by CRP[36]. There is also evidence that CRP increases the expression of plasminogen activator inhibitor type 1 (PAI-1) and decreases the expression of tissue plasminogen activator (t-PA)[37,38].

Inflammatory mediators, such as IL-6, increase platelet production. The newly formed platelets appear to be more thrombogenic. For example, the newly formed platelets activate at lower concentrations of thrombin[39]. Thus, both the platelet count and platelet reactivity are increased in response to inflammatory mediators.

Some authors have proposed the term "endothelial stunning" for the endothelial dysfunction/activation that may be induced by inflammatory cytokines and may thus play a key-role in the association between inflammation and VTE[40]. For example, CRP has been shown to induce the release of von Willebrand factor (vWF)[41] and to reduce the production of nitric oxide (NO) by endothelial cells[42].

As discussed above, in general for inflammatory diseases, there is also convincing evidence from basic science as well as clinical and epidemiological studies that IBD is associated with several prothrombotic abnormalities, including the initiation of the coagulation system, downregulation of natural anticoagulant mechanisms, impairment of fibrinolysis, increase in the platelet count and reactivity and dysfunction of the endothelium (Table 3)[43-45].

The mechanisms underlying IBD-associated prothrombotic abnormalities have been the subject of recent experimental and clinical studies. For example, Yoshida *et al*[46,47] showed that TNF-α and IL-1β are both implicated in the enhanced extra-intestinal thrombosis that accompanies experimental colitis [mice with dextran sodium sulphate (DSS)-induced colitis]. The authors noted that exogenous TNF-α and IL-1β enhanced thrombosis in the arterioles of control mice and that the enhanced thrombus formation in the arterioles of mice with DSS-induced colitis was significantly attenuated in wild-type colitic mice treated with TNF-α or IL-1β blocking antibodies and in colitic mice deficient for the TNF-α receptor or the IL-1 receptor. The IL-6 concentrations were positively correlated with disease activity and thrombocytosis in patients with UC[48]. Taken together, these data suggest that inflammatory cytokines such as TNF-α, IL-1β and IL-6 may play an important role in the inflammation-mediated risk of VTE in IBD.

Abnormalities of haemostasis associated with IBD

Abnormalities of coagulation: Quantitative alterations in key sites of the coagulation cascade that favour clot formation occur in patients with IBD[44]. These alterations include the elevation of circulating microparticles (including TF-rich microparticles)[49,50], factor Ⅶa[51], factors XIIa and XIa[52], factors Xa and Va[52,53], prothrombin[7,54-56] and fibrinogen[56,57]. The levels of antithrombin (AT) are significantly lower in the plasma of patients with IBD[56,58]. Reports on protein C and S deficiency in IBD are conflicting[48,59-61]. There is also a significantly lower expression of endothelial protein C receptor (EPCR) and thrombomodulin (TM), which impairs protein C activation leading to lower effective protein C activity[62]. TFPI levels were also shown to be reduced in patients with IBD[63,64]. Alterations suggestive of the activation of coagulation have also been reported in IBD. These include elevated prothrombin fragment 1+2 (prothrombin F1+2), thrombin-antithrombin (TAT) complexes, fibrinopeptide A (FPA) and B (FPB)[7,54-56] and decreased factor XIII levels[57,65].

IBD treatment was also found to influence coagulation abnormalities associated with IBD. For example, the treatment with infliximab induced a significant decrease in the amounts of circulating microparticles in IBD patients[49].

Abnormalities of fibrinolysis: The circulating concentration of factors involved in the lysis of clots also favours thrombosis in IBD. The plasma levels of t-PA are significantly lower in IBD patients than these levels in the general population[66,67]. There is also a significant absolute increase in urokinase-type plasminogen activator (u-PA) activity and a decrease in t-PA activity in the inflamed mucosa of IBD patients compared with the control group[66]. Two proteins that inhibit fibrinolysis,

Table 3 Controlled studies on the prevalence of inherited thrombophilias in inflammatory bowel disease

Ref.	Compared groups	Results							
		Mutation[1]	CD	UC	IBD	IBD-VTE	HC	C-VTE	Significance
Liebman *et al*[101], 1998 United States	11 IBD-VTE patients and 51 IBD patients without VTE	Factor V Leiden			4%	36%			Significant difference (OR = 14.00, 95%CI: 1.55-169.25)
Over *et al*[107], 1998 Turkey	63 IBD patients (20 CD and 43 UC patients) and 36 HC	Factor V Leiden	50%	20%			11%		Significant difference for CD *vs* HC (OR = 6.5, 95%CI: 1.3-18.0)
Haslam *et al*[112], 1999 United Kingdom	54 IBD patients (30 CD and 24 UC patients) and 55 HC	Factor V Leiden			9.3%		3.6%		Difference not significant
Heliö *et al*[111], 1999 Finland	563 IBD patients (235 CD and 328 UC patients) and 142 HC	Factor V Leiden	3.4%	5.2%	4.5%		2.1%		Differences not significant
		Factor XIII mutation	5.0%	6.1%	5.7%		3.3%		Differences not significant
Grip *et al*[6], 2000 Sweden	16 IBD-VTE patients, 99 C-VTE and 288 HC	Factor V Leiden				27%	11%	28%	Significant difference for IBD-VTE *vs* HC (OR = 3.0, 95%CI: 0.8-11.9)
		Prothrombin mutation				0%	1.8%	7.10%	Differences not significant
Koutroubakis *et al*[61], 2000 Greece	84 IBD patients (36 CD and 48 UC patients) and 61 HC	Factor V Leiden			8.3%		4.9%		Difference not significant
Papa *et al*[113], 2000 Italy	52 IBD patients (19 CD and 33 UC patients) and 156 HC	Factor V Leiden			1.9%		1.9%		Difference not significant
		Prothrombin mutation			1.9%		2.6%		Difference not significant
Vecchi *et al*[110], 2000 Italy	102 IBD (51 CD and 51 UC patients) and 204 HC	Factor V Leiden			1.5%		1.2%		Difference not significant
		Prothrombin mutation			1.1%		0.7%		Difference not significant
		MTHFR mutation			41.1%		47.4%		Difference not significant
Guédon *et al*[102], 2001 France	15 IBD-VTE, 58 IBD patients without VTE, 110 C- VTE and 84 HC	Factor V Leiden			0%	14.3%	3.6%	15.50%	Significant difference for IBD-VTE *vs* IBD ($P < 0.05$)
		Prothrombin mutation			1.7%	14.3%	3.6%	11.80%	Differences not significant
		MTHFR mutation			0%	0%	1.2%	0.90%	Differences not significant
Mózsik *et al*[106], 2001 Hungary	84 IBD patients (49 CD and 35 UC patients) and 57 HC	Factor V Leiden	14.3%	27.5%			5.3%		Significant difference for CD and UC *vs* HC ($P < 0.05$)
Nagy *et al*[108], 2001 Hungary	78 IBD patients (49 CD and 29 UC patients) and 57 HC	Factor V Leiden	14.3%	27.6%			5.3%		Significant difference for CD and UC *vs* HC ($P < 0.05$)
Turri *et al*[103], 2001 Italy	18 IBD patients with arterial or venous thrombosis, 45 IBD patients without thromboembolic events and 100 HC	Factor V Leiden			2.2%	0%	5%		Differences not significant
		Prothrombin mutation			0%	0%	2%		Differences not significant
Bjerregaard *et al*[120], 2002 Denmark	106 IBD patients and 4188 HC	Factor V Leiden			5.7%		6.7%		Difference not significant
		Prothrombin mutation							Difference not significant
Magro *et al*[119], 2003 Portugal	116 IBD patients (74 CD and 42 UC) and 141 healthy controls	Factor V Leiden	7%	2%			1%		Differences not significant
		G20210A Prothrombin	4%	0%			3%		Differences not significant
		MTHFR mutation	14%	12%			10%		Differences not significant
		PAI-1 mutation	11%	14%			24%		Differences not significant
Saibeni *et al*[121], 2003 Italy	152 IBD patients (62 CD and 90 UC patients) and 130 HC	Factor XIII mutation			5.3%		5.4%		Difference not significant
Törüner *et al*[118], 2004 Turkey	62 IBD patients (28 CD and 32 UC patients) and 80 HC	Factor V Leiden			3.2%		6.3%		Difference not significant
		Prothrombin mutation			0%		2.5%		Difference not significant
		MTHFR mutation			11.3%		6.3%		Difference not significant
Mahmood *et al*[117], 2005 United Kingdom	68 IBD patients (31 CD and 37 UC patients) and 30 HC	Factor V Leiden	0%	1.5%	1.5%		0%		Differences not significant
		Prothrombin mutation	0%	1.5%	1.5%		0%		Differences not significant

Oldenburg *et al*[98], 2005 Netherlands	22 IBD-VTE patients and 23 IBD patients without VTE	Factor V Leiden			0%	20%		Difference not significant
		Prothrombin mutation			8.7%	4.5%		Difference not significant
Spina *et al*[105], 2005 Italy	47 IBD-VTE patients and 94 C-VTE	Factor V Leiden				2.1%		13.8%	Significant difference for C-VTE *vs* IBD-VTE ($P < 0.05$)
		Prothrombin mutation				8.5%		12.8%	Difference not significant
Yilmaz *et al*[116], 2006 Turkey	27 IBD patients and 27 HC	Factor V Leiden			6.7%		5%		Difference not significant
		Prothrombin mutation			3.3%		6.7%		Difference not significant
		Factor XIII mutation			5%		0%		Difference not significant
		MTHFR mutation			3.3%		0%		Difference not significant
		PAI-1 mutation			11.7%		8.3%		Difference not significant
Bernstein *et al*[109], 2007 Canada	492 IBD patients (327 CD and 165 UC) and 412 HC	Factor V Leiden	6.4%	4.2%			6.1%		Differences not significant
		Prothrombin mutation	1.8%	1.2%			1.2%		Differences not significant
		Factor XIII mutation	8.7%	7.1%			4.3%		Significant difference for CD *vs* HC ($P < 0.05$)
		MTHFR mutation	12.5%	9.9%			11.7%		Differences not significant
Koutroubakis *et al*[104], 2007 Greece	30 IBD patients with vascular complications, 60 IBD patients without vascular complications, 30 controls with vascular complications and 54 HC	Factor V Leiden			6.7%	20.0%	3.7%	16.7%	Significant difference for IBD-VTE *vs* HC ($P < 0.05$)
		Prothrombin mutation			5.0%	10.0%	1.9%	13.3%	Differences not significant
		Factor XIII mutation			3.3%	0%	1.90%	0%	Differences not significant
		MTHFR mutation			11.6%	6.6%	7.5%	13.3%	Differences not significant
		PAI-1 mutation			20%		13.0%		Significant difference for IBD-VTE *vs* HC ($P < 0.05$)
Yasa *et al*[115], 2007 Turkey	27 IBD patients and 47 HC	Factor V Leiden			11.1%	43.3%	4.3%	36.7%	Difference not significant
		Prothrombin mutation			7.4%		0%		Difference not significant
		MTHFR mutation			14.9%		6.3%		Difference not significant
Maher *et al*[114], 2010 Saudi Arabia	26 IBD patients (7 CD and 19 UC patients) and 40 HC	Factor V Leiden			3.8%		2.5%		Difference not significant
Novacek *et al*[16], 2010 Austria	102 IBD patients (77 CD and 25 UC) and 102 HC	Factor V Leiden			16.1%		26.1%		Difference not significant
		Prothrombin mutation			1.7%		6%		Difference not significant

VTE: Venous thrombosis; CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; IBD-VTE: Inflammatory bowel disease with venous thrombosis; HC: Healthy controls; C-VTE: Controls with venous thrombosis; OR: Odds ratio. [1]Presented prevalence data refer to heterozygous and homozygous carrier for FV Leiden and prothrombin mutation and to homozygous carrier for the other mutations.

PAI-1[66] and thrombin-activatable fibrinolysis inhibitor (TAFI)[68], were found in higher concentrations in the plasma of IBD patients. Increasing levels of D-dimer, a fibrin degradation product, were also found in IBD, mainly in patients with active disease[58]. As D-dimer is generated from cross-linked fibrin, but not from fibrinogen, and elevated plasma concentration of D-dimer indicates recent or ongoing intravascular blood coagulation.

Abnormalities of platelets: In patients with IBD, there are often increased circulating platelet numbers and platelet and leukocyte-platelet aggregates (PLAs)[69]. Greater platelet aggregation has also been demonstrated in the mesenteric vasculature compared with non-IBD controls, supporting the hypothesis that platelet activity is stimulated in the mesenteric microcirculation[70]. Indeed, spontaneous platelet aggregation or platelet hypersensitivity to low levels of aggregating agents occurs in nearly one-half of patients with IBD[71] and appears to be independent of the disease activity[57,71]. Such platelet hyperactivation is mediated at least partly by the CD40-CD40L pathway, a key regulator and amplifier of immune-inflammatory reactivity and inducer of TF, which initiates the extrinsic coagulation pathway. Evidence for the involvement of CD40L includes a markedly elevated expression of CD40L protein by platelets from patients with IBD and the release of larger amounts of soluble CD40L into the plasma, leading to an approximately 15-fold increase in the CD40L plasma levels[72,73]. There are also elevated levels of CD40L in the mucosa that appear to be proportional to the degree of inflammation[72,74]. The activation of platelets in IBD may also be mediated by P-selectin.

IBD patients have been reported to have more platelets expressing P-selectin (marker of platelet activation) than healthy controls[69]. In the DSS model of murine colonic inflammation, colonic inflammation has been reported be associated with an increased number of circulating activated platelets, along with the formation of PLAs, which can be inhibited by selectin blockade with fucoidin[75].

The IBD treatment may influence platelet abnormalities associated with IBD. Infliximab significantly reduced plasma-soluble CD40L levels and eliminated CD40 from mucosal microvessels[76], whereas IBD patients on thiopurines had fewer PLAs than those not taking them[69]. These findings suggest that IBD treatment may influence platelet abnormalities associated with IBD.

Abnormalities of endothelium: Endothelial dysfunction has been clearly demonstrated in IBD patients and involves several aspects of endothelium biochemical physiology[77]. In particular, such dysfunction involves an alteration in the NO and reactive oxygen species (ROS) balance, which occurs when the endothelium fails to generate NO, a potent vasodilator and anti-aggregating agent, and instead forms elevated levels of superoxide anion[78]. Decreased NO generation may result from an acquired deficient transcription of nitric oxide synthase 2 (NOS2) in chronically inflamed IBD endothelium[79] and from the induction, by many inflammatory cytokines (*e.g.*, IL-2 and TNF-α), of the enzyme arginase, which competes with NOS[80]. The increased production of ROS in the inflamed endothelium may also contribute to oxidative stress in vWF molecules, which become unresponsive to proteolysis by ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), leading to the accumulation of ultra-large vWF multimers[81]. The latter are the most haemostatically active forms of vWF and, by favouring platelet adhesion and aggregation, may contribute to microvascular thrombosis in IBD. Increased levels of vWF were reported in IBD patients, especially in those with active disease[58,82].

Thrombophilia and IBD

Acquired risk factors: Antiphospholipid antibodies (APLA) and hyperhomocysteinaemia are two acquired thrombophilias associated with arterial and venous thrombosis. APLA are a group of prothrombotic antibodies directed against plasma proteins that are bound to anionic phospholipids. Patients with APLA may present with venous or arterial thrombosis, recurrent foetal loss and/or thrombocytopaenia. The disorder may be primary or may be associated with pregnancy or with inflammatory, post infectious and other disease states. This group of antibodies includes anti-cardiolipin (aCL), anti-β2-glycoprotein 1 (b2-GPI) and lupus anticoagulants, each of which requires specific testing. Available studies in IBD vary in the assessment of different antibodies, types of IBD and disease activity level; therefore, the true prevalence of APLA in IBD patients remains unclear. The prevalence of aCL antibodies in IBD patients is higher than in the control population, with an average incidence of 20%-30%, but the association with thrombosis in IBD patients is less clear[83]. Similarly, the levels of antibodies against b2-GPI, the cofactor that mediates the binding of aCL antibodies to cardiolipin and a more specific measure of the risk associated with thrombosis, has been detected in 9% of patients with IBD compared with its absence in healthy controls[84]. Lupus anticoagulants were not detected in a small series of 16 patients with CD[85]. The levels of aCL antibodies and anti-b2-GPI antibodies and of lupus anticoagulants were similar in a population of IBD patients with and without current or past VTE events[84,86]. One of the causes of the appearance of APLA in IBD may be anti-TNF-α therapy because this therapy has been associated with the development of APLA[87,88].

Hyperhomocysteinaemia may be both a genetic and acquired abnormality. The most common genetic defect is homozygosity for a thermolabile mutant of the enzyme methylenetetrahydrofolate reductase (MTHFR)[89]. Plasma homocysteine concentrations can also be increased by deficiencies in vitamin B6, B12 or folic acid (dietary, genetic or drug-associated)[90]. Hyperhomocysteinaemia is an independent risk factor for atherosclerotic vascular disease, with the risk increasing in a graded fashion with increasing plasma homocysteine concentrations[91,92]. Hyperhomocysteinaemia has also been associated with an increased risk of VTE[93,94]. Reducing levels of homocysteine with B vitamin supplements, however, has not resulted in a reduction in the incidence of recurrent VTE or arterial thrombotic complications[95,96]. The association of folate deficiency and hyperhomocysteinaemia has been evaluated in IBD patients. One study reported elevated serum homocysteine and low folate in 63 patients with IBD, but these levels were not observed in 183 matched controls without thrombotic complications[97]. In a small study, fasting homocysteine levels in IBD patients with a history of arterial or venous thrombosis tended to be higher (although not significantly) than in IBD controls[98]. Recently, Oussalah *et al*[99] conducted a systematic review and meta-analysis to evaluate the association between homocysteine metabolism and IBD and the association between hyperhomocysteinaemia and thrombosis in IBD. The mean plasma homocysteine level was significantly higher in IBD patients compared with the controls. The mean plasma homocysteine level did not differ between patients with UC and CD. The risk of hyperhomocysteinaemia was significantly higher in IBD patients compared with controls (OR = 4.65, 95%CI: 3.04-7.09). The risk of hyperhomocysteinaemia was not higher among IBD patients who experienced thromboembolic complications (OR = 1.97, 95%CI: 0.83-4.67), suggesting that hyperhomocysteinaemia may not be a major contributor to VTE in IBD. Medication-associated folate deficiency (*e.g.*, methotrexate or sulfasalazine) may be the most common explanation for hyperhomocysteinaemia in IBD patients, although deficiencies in vitamin B6 and B12 and a MTHFR mutation may also play a role

(see below). Taken together, the current data do not support a major role for APLA or hyperhomocysteinaemia in IBD-associated VTE, but studies with a higher number of patients and a prospective design are needed.

Inherited risk factors: A summary of controlled studies on the prevalence of inherited thrombophilias in IBD is presented in Table 3. The rate of inherited thrombophilias in patients with IBD and VTE is estimated to be 15%-30%, which is similar to the rate in non-IBD patients and VTE in most studies[6,17,25,98,100-104], although one study has reported a lower rate of inherited thrombophilias in patients with IBD and VTE[105]. Data comparing the prevalence of inherited thrombophilias in the overall IBD population and in the general population are conflicting. Although some cohorts reported a higher prevalence in the overall IBD population[106-109], most reported a similar prevalence[6,16,61,102-104,109-121]. These data suggest that the role of inherited thrombophilias in VTE in IBD patients is similar to that in the general population.

The most prevalent thrombophilia reported in IBD patients is factor V mutation. Other genetic variants that have been found in IBD patients include the prothrombin G20210A mutation, deficiencies in protein C, protein S and antithrombin, the PAI-1 4G mutation, the factor XII val34leu mutation and the MTHFR C677T mutation (Tables 2 and 3). Factor V mutation increases the risk of thrombosis five- to eightfold for heterozygous carriers and 50- to 80-fold for homozygous carriers[122]. A similar frequency of factor V Leiden was reported in IBD patients with thrombosis compared with thrombotic controls[6,102,104] and in the overall IBD population compared with the general population[61,109]. However, the prevalence of factor V mutation in thrombotic IBD patients has been shown to be significantly higher than that in IBD patients without thrombosis, suggesting that factor V Leiden, when present, increases the risk of IBD-associated VTE[101,102]. Two recent meta-analyses confirmed this conclusion. In the meta-analysis of Zhong *et al*[123], the OR of VTE in IBD patients with factor V mutation was higher than in IBD patients (OR = 4.00, 95%CI: 2.04-7.87) and healthy controls (OR = 3.19, 95%CI: 1.38-7.36). Liang *et al*[124] showed a similar prevalence of factor V mutation in IBD patients and the general population (summary OR = 1.13, 95%CI: 0.87-1.46). Of note, the factor V Leiden mutation was associated with a significantly higher risk of thromboembolism in IBD patients (summary OR = 5.30, 95%CI: 2.25-12.48)[124].

The prothrombin G20210A mutation leads to greater prothrombin plasma levels (heterozygous carriers have approximately 30% higher PT levels than healthy controls) and increases the risk of VTE approximately threefold[122]. There is no difference in the prevalence of the prothrombin G20210A mutation between IBD patients and normal controls[110,120], between IBD patients with thrombosis and non-IBD patients with thrombosis[6,102] or between IBD patients with and without thrombosis[102,104]. Protein C, protein S and antithrombin Ⅲ deficiencies also have no increased prevalence among patients with IBD, regardless of whether they have had a VTE[52,125-127].

The factor XIII val34leu mutation is associated with a greater FXIII activation rate and leads to a 20%-40% reduction of the risk of VTE for homozygous carriers[111,121]. A slightly greater prevalence of factor XIII (val34leu) mutation carriers in CD was found in a recent population-based study[109], but this prevalence could not explain the greater risk of VTE in CD. Available data suggest that there is no difference in the prevalence of homozygous carriers of the factor XIII val34leu mutation between IBD patients and healthy controls[111,116,121]. Finally, the prevalence of the factor XIII val34leu mutation was similar in thrombotic IBD patients and non-IBD thrombotic patients[104].

The MTHFR C677T mutation leads to a 25% increase in homocysteine plasma levels in homozygous carriers[128]. The effect of the MTHFR C677T mutation on the risk of VTE varies among studies, and a recent meta-analysis found a weak effect (20% risk increase)[128]. The prevalence of the MTHFR C677T mutation in IBD has shown discordant results, most likely because of regional and ethnic variations in the prevalence of this polymorphism in the general population. The allelic frequency of MTHFR C677T has been reported to be higher in IBD patients than in the reference population[119]. In a recent population-based case-control study, some differences were observed between patients with IBD and healthy controls (with a decreased number of mutant allele carriers in UC); however, these differences did not explain the excess risk of thrombosis[109]. No difference in the prevalence of homozygous carriers of the MTHFR C677T mutation was found between the IBD patients and healthy controls in most studies[102,104,109,110,115,116,118,119]. The prevalence of C677T homozygosity between IBD thrombotic patients and non-IBD thrombotic patients showed no significant difference[102,104].

Several studies have demonstrated that the PAI-1 (4G) homozygosity is associated with enhanced PAI-1 expression[129] and contributes as an additional risk factor towards the development of VTE[130]. However, the evidence regarding the relationship between an elevated PAI-1 plasma level or PAI-1 4G polymorphism and the risk of VTE is rather conflicting. The allelic frequency of PAI-1 4G has been reported as being higher in IBD patients than in the reference population[119]. Moreover, a recent study showed a significantly higher allelic frequency of PAI-1 4G in IBD patients with vascular complications compared with IBD patients and healthy controls[104]. No difference in the prevalence of homozygous carriers of the PAI-1 4G mutation was found between IBD patients and healthy controls in most studies[104,116,119]. The prevalence of this genotype does not differ in thrombotic IBD patients compared with non-IBD thrombotic patients[104].

As in the general population, more than one thrombotic defect can occur among IBD patients with inherited thrombophilia, particularly factor V Leiden[104,119]. A higher prevalence of the carriage of two or more throm-

bogenic polymorphisms has been found in IBD patients compared with the reference population[119], but no significant difference has been found between thrombotic and non-thrombotic IBD patients[104].

Taken together, these data show that genetic risk factors are generally not found more often in IBD patients than in others, suggesting that genetics does not explain the greater risk of VTE in CD and UC. However, when genetic risk factors occur, patients with IBD (compared with healthy controls) are more likely to suffer thromboembolic complications, suggesting that hereditary thrombophilia and inflammation-associated thrombogenicity have at least an additive effect for the risk of VTE in IBD.

PHARMACOLOGICAL EFFECT ON RISK FACTORS

Almost all drugs used in the treatment of IBD have been associated with abnormalities in the haemostatic system in experimental and clinical studies. Corticosteroids have been associated with both hypo- and hypercoagulating alterations[131,132]. A meta-analysis demonstrated that dexamethasone-based chemotherapy was a risk for VTE in patients with multiple myeloma[133]. Furthermore, in a large cohort of surgical IBD patients, the use of steroids was identified as a potentially modifiable risk factor for postoperative VTE in IBD patients[24]. Studies of platelets from IBD patients treated with 5-aminosalicylic acid (5-ASA) agents have shown conflicting results. *In vitro*, 5-ASA significantly reduced both spontaneous and thrombin-induced platelet activation[134]. *In vivo,* platelets from IBD patients taking 5-ASA have decreased expression levels of P-selectin, a surface marker for platelet activation[134], and lower plasma levels of RANTES (Regulated upon Activation Normal T-cell Expressed and Secreted), a prothrombotic platelet cytokine[135]. In contrast to these findings, a study of six patients with IBD (four with UC and two with CD) treated with 5-ASA showed no changes in platelet aggregation or fibrinolytic activity[136]. Sulfasalazine inhibits dihydrofolate reductase leading to folate deficiency, which is a cause of hyperhomocysteinaemia (acquired thrombophilia; see above). Plasma homocysteinemia levels have been reported to be significantly increased in patients with ankylosing spondylitis under sulfasalazine therapy[137].

Azathioprine has been shown to inhibit platelet aggregation *in vitro*[138]. IBD patients taking thiopurines experienced fewer PLAs than patients who were not taking them[69]. The *in vitro* data suggest an antithrombotic effect from azathioprine and 6-mercaptopurine. Methotrexate, a folate antagonist, is a well-established contributor to hyperhomocysteinaemia (which is associated with thrombosis risk) when used in patients with rheumatoid arthritis[139]. Nonetheless, no study associating methotrexate with hyperhomocysteinaemia is available for IBD. Cyclosporine has been associated with thrombogenicity *in vitro* and *in vivo*. *In vitro* studies showed an increased platelet aggregation[138] and activation of endothelial cells[140] induced by cyclosporine. Cyclosporine has also been associated with impaired fibrinolysis through a decrease in PAI-1 activity[141]. The *in vitro* thrombogenicity of cyclosporine has been confirmed *in vivo* by several studies showing thrombotic events in patients taking cyclosporine[142].

Infliximab, an antibody against anti-TNF-α, may decrease platelet activity through the downregulation of the CD40/CD40L pathway in the mucosal microcirculation[76]. Additionally, in patients with active rheumatoid arthritis, infliximab treatment has been shown to normalise the disease-associated impairment of the coagulation and fibrinolytic systems by decreasing the levels of prothrombin F1+2 and D-dimer[143], t-PA antigen, PAI-1 antigen and PAI-1 activity[144]. Finally, infliximab induced a significant decrease in the amounts of circulating microparticles in IBD patients[49]. Despite these potential anticoagulant effects of the TNF-α blockade, there are also case reports of thrombosis at several sites, such as the retinal vein, in patients under anti-TNF-α therapy[145]. Moreover, the prothrombotic effects of anti-TNF-α therapy may be mediated by antiphospholipid antibodies (acquired thrombophilia) as anti-TNF-α therapy has been associated with the development of APLA[87,88]. Nonetheless, a recent prospective observational cohort study of biological safety in patients with rheumatoid arthritis showed that VTE events are not increased in patients with rheumatoid arthritis who are treated with anti-TNF therapy[146].

CONCLUSION

In IBD, there is an increased risk of thromboembolic events due to inflammation, nutritional deficiencies, hospitalisations, surgery and inherited prothrombotic factors. Moreover, beyond an increased risk, VTE may have clinical specificities in IBD. There is evidence that subjects with IBD experience the first episode of VTE early in life[6]. In IBD, the RR of VTE is inversely correlated with age (*i.e.*, younger IBD patients have a higher RR of VTE); nevertheless, the actual incidence increases with age[8,11,13,21]. The rate of recurrent VTE in the five years after the discontinuation of anticoagulation therapy is also increased in IBD [adjusted RR (aRR) = 2.5, 95%CI: 1.4-4.2][16]. Even with continued prophylaxis for VTE, the risk of recurrence of VTE in IBD patients has been reported to be 13%[17]. Low molecular weight heparin (LMWH) has been shown to be less effective in preventing DVT in hospitalised subjects undergoing surgery for IBD than in patients with non-IBD conditions, including colorectal cancer and diverticular disease (aOR = 5.9, 95%CI: 0.9-39.7, for UC and DVT postoperatively)[147]. Importantly, VTE appears to carry a poorer prognostic outcome for patients with IBD than for the general population. In a hospitalised cohort, the rate of VTE was not only higher in IBD subjects than in the controls, but the admissions for IBD subjects were also longer (11.7 *vs*

6.1 d, $P < 0.0001$) and were associated with higher costs ($47515 *vs* $21499, $P < 0.0001$) and higher mortality (aOR = 2.5, 95%CI: 1.83-3.43)[12].

Therefore, clinicians should be aware of these risks so that adequate prophylactic actions can be taken in all IBD patients with flares, particularly in patients who are hospitalised, submitted to surgery or undergoing treatment.

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