Format for ANSWERING REVIEWERS

November 04, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5382-review.doc).

Title: Inflammatory bowel disease: epidemiology, pathology and risk factors for hypercoagulability

Author: Danuta Owczarek, Dorota Cibor, Mikołaj K. Głowacki, Tomasz Rodacki, Tomasz Mach.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5382

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

1. Tables 1 and 2 that show abnormalities of coagulation and fibrinolytic system, as well as acquired prothrombotic factors in IBD patients have been introduced to the paper.

Table 1. Acquired prothrombotic factors in IBD

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

Table 2. Changes in coagulation and fibrinolytic systems in patients with IBD.

Coagulation factors	**Fibrinolytic factors**	**Plasma coagulation inhibitors**
fibrynogen ↑ Factor V ↑ Factor VII ↑ Factor VIII ↑ Factor XI ↑ prothrombin fragment 1+2 ↑ thrombin-antithrombin complex ↑ TF ↑ F XIII ↓	TAFI ↑ PAI-1 ↑ tPA ↓	Antithrombin III ↓ TFPI ↓

tPA - tissue plasminogen activator
TAFI - thrombin-activatable fibrinolysis inhibitor
PAI-1 - plasminogen activator inhibitor 1
TFPI - tissue factor pathway inhibitor

2. The graphs presented in our paper have been corrected as suggested by the reviewers. Changes in fibrinolytic and coagulation systems in IBD patients have been highlighted.

3. Additional information about TE in children with IBD has been provided.

"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 year of age, though the actual incidence increased with age[16]. A higher incidence of cerebral TE in pediatric population with IBD was noticed, as well[17]".

4. Information about the potential use of heparin has been added.

"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 the 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]."

5. The role of antithrombin III in IBD is still under investigation and no firm conclusions could be drawn weather its decrease is associated with disease activity.

6. The potential influence of medications used in IBD on the hemostatic system has been described.

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

It has been confirmed by many studies that glucocorticoids increase the risk of VTE[67]. Johannesdottir et al. 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[67]. Glucocorticoids also inhibit oral anticoagulants.

Data regarding coagulation and the use of anti TNF antagonists are conflicting. For instance, in a national prospective observational cohort study in Great Britain, the 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 complement 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 a decrease in the effect of warfarin, what might be caused by reduced bioavailability, enhanced warfarin metabolism, or increased prothrombin activity[70]".

7. Additional information about TE in pregnancy has been provided.

"In the majority of women, pregnancy is uncomplicated[14]. No higher risk of TE was observed in pregnant women[15]."

8. A section about the use of thromboprophylaxis in IBD has been added.

"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) suggest 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 the 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]."

9. The section "Conclusion" has been rearranged.

"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".

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Danuta Owczarek, MD, PhD
Dept. of Gastroenterology, Hepatology and Infectious Diseases
Jagiellonian University Medical College
Cracow, Śniadeckich 5
31-531 Poland
Fax: +48-12-424-7380
E-mail: owczarek@su.krakow.pl