Exploring the relationships between inflammatory response and coagulation cascade in inflammatory bowel disease

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Abstract. – *Background:* The inflammatory network and the coagulation cascade are strictly correlated biological systems. Inflammatory Bowel Diseases (IBD) are characterised by a prothrombotic state, a hypercoagulability state and an increased prevalence of thromboembolic events.

Methods: We reviewed the IBD literature in which the relationships between inflammation and coagulation were evaluated.

Results: Several risk factors and mechanisms have been suggested to be implicated in determining the increased risk for thrombosis of IBD. Even if IBD may be per se a prothrombotic condition, systemic inflammation and vitamin deficiencies appear to play a relevant role in determining such a risk.

Conclusions: A good and continuous control of the intestinal disease and vitamin supplementation are strongly recommended in order to correct some of the risk factors for thrombosis in IBD patients.

Key Words:

Inflammation, Coagulation, Inflammatory bowel diseases, Thrombosis.

Introduction

In recent years it has been demonstrated that a looping interaction exists between inflammatory response and coagulation cascade; it has also been established that the activation of coagulation acts as a constituent of the inflammatory response directly mediating cytokine response[1-3] and that some proinflammatory cytokines, such as Interleukin-6 (IL-6), induces coagulation activation[4,5]. Fibrinolysis is also strictly related to inflammatory response; in particular, it appears that hypofibrinolysis, a prothrombotic condition, is a typical feature of inflammation[6].

The most intriguing new insights in the interrelations between inflammation and coagulation arise from the natural anticoagulant system formed by protein C (PC) and its cofactor protein S (PS). In particular, recent research into the protein C pathway has provided insights into its anti-inflammatory role, particularly that of activated protein C (APC)[7]. The Endothelial Protein C Receptor (EPCR) and thrombomodulin (TM) are two receptors, down-regulated by inflammatory cytokines[7], that facilitate protein C activation in arteries and veins and thus maintain the antithrombotic potential of the vessel surfaces. In the last years, it has been demonstrated that the PC-TM-EPCR system has relevant activities also on inflammation, by means of several actions[8]. The most important clinical evidence is provided by the significant decrease of mortality in patients with severe sepsis treated with APC[9].

The chronic inflammatory nature as well as the clearly recognised increased risk for venous and arterial thrombosis of Inflammatory Bowel Disease (IBD)[10] explain the impressive number of studies and the extensive investigations performed on coagulation profile and risk factors for thrombosis in Crohn's disease and in ulcerative colitis. However, despite several qualitative and quantitative alterations both in the coagulation and the fibrinolysis systems have been described, the mechanisms of this complication in IBD are still incompletely elucidated.

In this brief summary, we mainly considered those studies which investigated conditions and molecules strictly related to inflammation.

Results

In general, the interpretation of the studies of haemostatic variables is made difficult by several factors, such as intra- and inter-assay variabilities of the different tests, pre-test circumstances (i.e., modalities of sampling) and laboratory handling that may influence the results[11]. In IBD, the comparisons of the different studies are further complicated by other factors, such as differences in the clinical and demographic features of the patients studied and in the disease activity evaluation.

Despite these limitations, both the prothrombotic nature and the hypercoagulability state are established features of IBD as well as the implication of endothelial cells.

The prothrombotic condition is identified as an increase in risk factors for thrombosis and/or a decrease in the natural anticoagulant factors. In IBD, an increased prevalence of several recognised risk factors for thrombosis, which are also considered acute-phase reactants, have been repeatedly described, such as increased levels of Factor VIII[10], lipoprotein (a)[12], fibrinogen[12], platelets[13] and decreased levels of vitamin B_6[14]. A decrease in the natural anticoagulant factors, such as antithrombin III (AT III), PC-PS, and Tissue Factor Pathway Inhibitor (TFPI) has also been described in IBD. Data about decreased AT III plasma levels appear to be the most consistent, possibly due to consumption, while PC plasma levels appear unchanged[15]. Also PS and TFPI plasma levels, the second markedly in active diseases, appear to be decreased, but few data exist in literature[15,16].

As described above, a prothrombotic condition may also result from a reduced fibrinolytic activity, and hypofibrinolysis has been described during IBD[17,18]. We studied a recently identified molecule of the fibrinolytic system: Thrombin Activatable Fibrinolysis Inhibitor (TAFI); it has been suggested that increased levels of TAFI represent a risk factors for thrombosis. In our study, we showed that TAFI plasma levels are increased in IBD patients and correlate with acute-phase reactants[19]. This finding suggests the possible induction of a hypofibrinolytic state which, as we know, represents a prothrombotic condition.

The hypercoagulability state, instead, identifies an unbalancing in the coagulation cascade towards the procoagulant forces due to an excessive activation of the coagulation enzymes without clinical signs of thrombosis. Several authors studied the most sensitive markers of coagulation activation, such as prothrombin Fragment 1 + 2 (F 1 + 2), Thrombin-Antithrombin III complex (TAT), fibrinopeptide A (FPA) and fibrinopeptide B (FPB), showing findings compatible with subclinical activation of coagulation in IBD[15,20-22]. It is debated if this evidence of activation of coagulation is secondary to inflammation or is a feature of IBD, independent of disease activity and of resective surgery[23,24].

Evidences of the activation of the blood coagulation are also provided by the decrease of Factor XIII (FXIII) plasma concentrations; indeed, reduced levels of FXIII have been frequently described during active IBD, while they appear to be unchanged in quiescent IBD[25,26]. Also an increase of fibrinolityc activity may be used as a likely evidence of activated coagulation. A "reactive" hyperfibrinolysis has been described in IBD patients, mainly during the active phases of the disease[27,28].

Finally, markers of endothelial damage, such as von Willebrand Factor (vWF) and thrombomodulin (TM), are increased in serum of IBD patients, with possible correlation with disease activity and/or acute phase reactants[15,29-31]. It has been debated whether intestinal vascular involvement observed in IBD is the *primum movens* of these diseases[32] or a consequence, with amplification, of the local and/or systemic inflammation[33].

Recently, we published a paper about EPCR and TM in IBD patients[34]. According to our findings, the expression of EPCR and TM is reduced in the intestinal tissue of IBD patients resulting in a reduced potential for protein C activation in the mucosal vessels and, consequently, in an increased risk for local microthrombosis. In our opinion, this decrease is probably part of the inflammatory response observed in IBD and not a primary alteration. We also observed increased levels of plasma soluble TM and EPCR in IBD patients; since we did not find any association with disease activity, we interpreted this finding as the possible expression of the chronic inflammation and vascular involvement characteristic of these diseases.

Discussion

Thromboses are complex events, in whom several mechanisms and causal factors are implicated; for example, in IBD one should consider disease activity, surgical interventions or prolonged inactivity. Moreover, the blood alterations observed during a thrombotic event may be the consequence, rather than the causes, of thrombosis.

Even though literature data about haemostatic parameters and risk factors for thrombosis in IBD are not always univocal and results are not always reproduced in the different studies, evidences appear quite in agreement in conferring to inflammation, and then to clinical activity, a consistent role in determining the prothrombotic condition and the hypercoagulability state typically observed in IBD[11]. This is in agreement with the mounting body of evidence which is clarifying the strong links existing between inflammation and thrombosis[35-37].

A confirmation to the relevant role played by inflammation is provided by the finding that thromboses complicating IBD course appear to be more frequent during the phases of activity of these diseases[12,38]. In IBD, inflammation may lead to the increased risk for thrombosis through several pathways, i.e. by activating coagulation cascade, by decreasing anti-coagulant activity, by inducing hypofibrinolysis and by determining malabsorption and hypercatabolism with consequent vitamin deficiencies that, in turn, may lead to hyperhomocysteinemia, a well-known risk factor for thrombosis[39].

However, it is also true that coagulation abnormalities as well IBD-related thromboses may occur during clinically quiescent diseases or even before the diagnosis of the intestinal disease; thus, IBD could represent *per se* a condition favouring thrombosis.

Some clinical consequences may derive from these data: when one is managing an IBD patient, he (she) should always keep in mind that the patient is at increased risk for thrombosis; thus, every effort should be addressed to avoid this complication which affects young people and is an important cause of morbidity and mortality[40]. As a consequence, a good and continuous control of disease activity is strongly recommended in IBD patients as well as vitamin supplementation.

Moreover, prophylactic anti-thrombotic treatment should be started in all the conditions which are associated with an increased risk for thrombosis, such as prolonged inactivity or surgical interventions.

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