of IBD. Multifocal intestinal infarction with vascular injury, focal arteritis, and fibrin deposition, in association with granulomatous or lymphocytic inflammation, are common findings in chronic inflamed gut mucosa. Also microvascular endothelial dysfunction with diminished vasodilatory capacity seems to be a feature of intestinal microvessels in IBD, by contributing to reduced perfusion, impaired wound healing and maintenance of chronic inflammation.

Moreover, patients with inflammatory bowel disease (IBD) frequently suffer from thromboembolic events which represent an important cause of morbidity and mortality. The incidence of systemic thromboembolism (TE) in IBD ranges between 1 and 7.7% in clinical studies, rising to 41% in postmortem studies. These differences in incidence are probably attributable to the fact that the autopic studies are dated about 40-50 years ago when the management of IBD was more aggressive and TE prophylactic therapy not yet standardized. However, a recently performed population-based study has shown that IBD patients have a 3-fold increased risk of developing deep venous thrombosis and pulmonary embolism compared to the general population. Moreover, patients with inflammatory bowel disease (IBD) frequently suffer from thromboembolic events which represent an important cause of morbidity and mortality. The incidence of systemic thromboembolism (TE) in IBD ranges between 1 and 7.7% in clinical studies, rising to 41% in postmortem studies. These differences in incidence are probably attributable to the fact that the autopic studies are dated about 40-50 years ago when the management of IBD was more aggressive and TE prophylactic therapy not yet standardized. However, a recently performed population-based study has shown that IBD patients have a 3-fold increased risk of developing deep venous thrombosis and pulmonary embolism compared to the general population. This finding has been confirmed in another study showing that TE is a specific feature of IBD as neither rheumatoid arthritis, another chronic inflammatory disease, nor celiac disease, another chronic bowel disease, had an increased risk of TE compared to control subjects. On the contrary, no increased incidence of venous thrombosis was reported in a population of 1253 Swedish IBD patients compared to the

**Abstract.** – Patients with inflammatory bowel disease (IBD) have an increased risk of thrombotic complications. Arterial and venous system may be involved. Moreover, mesenteric microvascular thrombosis has been hypothesised as a contributing factor in the pathogenesis of IBD.

Early atherosclerosis is a clinical feature common to several inflammatory and immunological diseases in which atherothrombotic complication represents one of the most important cause of mortality and morbidity. We investigate the prevalence and the entity of the early stages of vascular disease in a population of IBD patients without the classical cardiovascular risk factors, by measuring the intima-media thickness (IMT) of the common carotid artery. We found that IBD patients have an increased risk of early atherosclerosis than healthy controls as showed by greater values of carotid IMT and that homocysteine levels and age were independently associated with the increased arterial wall thickness.

**Key Words:** Inflammatory bowel disease, Vascular disease, Atherosclerosis, Homocysteine.

**IBD and Vascular Disease**

Crohn’s disease (CD) and ulcerative colitis (UC) are the two major forms of chronic inflammatory bowel disease (IBD). Although their aetiology still remains unknown, mounting evidence suggests that gut tissue injury is the result of an abnormal immune response and involves multiple non immune cellular systems, including intestinal microvascular endothelial cells. Indeed, it has been proposed that mesenteric microvascular thrombosis may be implicated in the pathogenesis of IBD. Multifocal intestinal infarction with vascular injury, focal arteritis, and fibrin deposition, in association with granulomatous or lymphocytic inflammation, are common findings in chronic inflamed gut mucosa. Also microvascular endothelial dysfunction with diminished vasodilatory capacity seems to be a feature of intestinal microvessels in IBD, by contributing to reduced perfusion, impaired wound healing and maintenance of chronic inflammation.
background population\textsuperscript{14}. However, TE in patient cohort occurred earlier in life in IBD patients than non-IBD patients (53 versus 64 years). Arterial and venous system may be involved. TE occurs more often in the deep vein of the leg and pulmonary circulation, but it has been described, less frequently, in other sites such as the cerebrovascular system, portal vein, mesenteric veins and retinal vein\textsuperscript{15}. Arterial TE complications occur less frequently in patients with IBD than venous TE and mainly after surgery. The complications include thrombosis of retinal, cerebral and renal arteries, but also the arteries of the upper and lower limbs may be involved\textsuperscript{16-18}. Also some cases of thrombosis of coronary arteries in young patients\textsuperscript{19} and aortic mural thrombi have been reported\textsuperscript{20}. IBD activity and extent of disease, particularly pancolonic involvement in UC patients, positively correlate with venous thromboembolic risk. In fact, in a recent revision of IBD patients with deep venous thrombosis (DVT) or pulmonary embolism (PE) evaluated at Mayo Clinic Rochester in a decade (1990-2000), about 80\% of patients had active disease at the time of DVT/PE and about tree-quarters of patients with UC had entire colonic involvement\textsuperscript{21}. However, it is noteworthy that in a large study one third of thromboembolic complications occurred during disease quiescence, supporting the hypothesis of an increased procoagulant tendency in IBD, independent of disease activity\textsuperscript{1}.

Indeed, it is not known whether hypercoagulability in IBD is an epiphenomenon secondary to chronic intestinal inflammation or, in turn, may play a central role in the pathogenesis of IBD.

Additional indirect evidence that vascular thrombosis could be involved in IBD pathogenesis is provided by an epidemiological study performed on a large cohort of subjects with hemophilia or von Willebrand’s disease\textsuperscript{22}. In this population, IBD occurred less frequently than expected, and it has been suggested that inherited disorders of coagulation might be protective against IBD. Finally, the potential therapeutic value of unfractioned heparin as well as low molecular weight heparin, especially in UC, provides further clues that a “hypercoagulable state” could contribute in pathogenesis of IBD\textsuperscript{23}.

### Early Atherosclerosis in Immunological Diseases

Early atherosclerosis is a clinical feature common to several inflammatory and immunological diseases in which atherothrombotic complication represents one of the most important cause of mortality and morbidity\textsuperscript{24,25}. In particular, in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) there is growing recognition of an excess mortality which is predominantly due to increased coronary and cerebral artery atherosclerosis\textsuperscript{26,27}.

To investigate the prevalence and the entity of the early stages of vascular disease, in the last decade, have been proposed and validated several methods, such as the assessment of the intima-media thickness (IMT) of the wall of the common carotid artery by high-resolution ultrasonography\textsuperscript{28}. This method has been shown to predict the occurrence of cardiovascular events\textsuperscript{29,30} and has been extensively used in studies carried out in populations at high risk for vascular disease, such as in subjects affected by type 1 and 2 diabetes mellitus, familial hypercholesterolemia and uremia but also in immune disorders\textsuperscript{31-34}. In particular, patients affected by RA and SLE showed carotid IMT values significantly increased compared to control populations\textsuperscript{25,31,33,34}.

Recent studies have focused on the role of inflammation in the development and progression of atherosclerosis\textsuperscript{35-37} and, in turn, accelerated atherosclerosis was found in inflammatory and immune disorders such as SLE and RA\textsuperscript{26,27}. Chronic inflammation may act independently or synergistically with traditional atherosclerotic risk factors in the pathogenesis of atherosclerosis and may also be associated with a hypercoagulable state.

### Early Atherosclerosis in IBD

We investigated the hypothesis that IBD patients would have subclinical morphologic evidence of atherosclerosis, trying to identify the potential risk factors associated with vascular disease. The studied groups were constituted of 52 patients (18 had UC and 34 CD) and 20 controls matched to the patients
for age and sex. The enrolled patients hadn’t previous cerebrovascular events or the classical risk factors for atherothrombotic disease, such as: diabetes, hypertension, smoking, and dyslipidemia. The carotid arteries were evaluated with high-resolution B-mode ultrasonography using an echotomographic system (Acuson 128 XP/10 ART; Acuson, USA) with a 7 MHz linear transducer. IMT was measured on the far wall at 5, 10 and 15 mm proximal to the carotid bifurcation over both right and left common carotid arteries. The IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line (Figure 1). The mean IMT, defined as the mean of the six measurements (three for each side), was considered for statistical analysis. Mean carotid IMT value was significantly higher in IBD patients (0.63 ± 0.15 mm) than in controls (0.53 ± 0.08 mm) (P = 0.008).

Among the relevant potential predictors of increased IMT only plasma homocysteine and age showed a positive correlation at univariate analysis while body mass index, CRP, ESR, total HDL and LDL cholesterol, triglycerides, systolic and diastolic blood pressure resulted not associated with IMT of the common carotid arteries Multiple regression analysis confirmed the association of age and homocysteine with IMT.

It is known that hyperhomocysteinemia is a risk factor for arterial as well as venous thrombosis58-41. Interestingly, increased levels of homocysteine were found in the circulation42-46 and intestinal mucosa of IBD patients47,48 and, it has been speculated that hyperhomocysteinemia may account for the increased thrombotic risk observed in IBD and contribute to the inflammatory state of the mucosal IBD endothelium47. Elevations in homocysteine levels are typically associated with low serum levels of folate, vitamin B12, and B6 that are essential cofactors for the enzymes involved in the metabolism of homocysteine42-45,49 or can be caused by genetic polymorphisms of the enzymes involved in homocysteine metabolism40,41.

However, the mechanisms through which hyperhomocysteinemia promotes vascular disease remain an active area of research. In atherosclerosis, homocysteine is recognized as a key inflammatory molecule that induces endothelial cell damage, impairs flow-mediated arterial dilation, and triggers vascular inflammation50-54. Thus, inflammatory mechanisms seem implicated not only in the pathogenesis of chronic rheumatological and intestinal inflammatory disorders, such as RA and IBD but also in atherosclerotic vascular disease. The shared features include among the others, the involvement of proinflammatory cytokines such as the tumor necrosis factor (TNF)-α and interleukin-6, raised concentrations of CRP, increased local expression of adhesion molecules, neoangiogenesis, and the CD40 pathway. Moreover, infliximab, an anti-TNF-α monoclonal antibody recently used in the treatment of RA and CD, is able to improve not only the inflammatory process but also the endothelial function, as reported in RA patients55. In the present study, the sub-group of patients treated with infliximab showed values of IMT that did not differ from those of healthy controls, so that a beneficial effect of infliximab is plausible. In conclusion, we reported the evidence of subclinical atherosclerosis in IBD patients, as demonstrated by greater IMT of the common carotid artery compared with healthy subjects. Homocysteine levels and age were the most important factors associated with increased IMT in our cohort of IBD patients.
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