IS THERE A CARDIOVASCULAR RISK IN INFLAMMATORY BOWEL DISEASES?

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IS THERE A CARDIOVASCULAR RISK IN INFLAMMATORY BOWEL DISEASES? (Abstract): Inflammatory bowel diseases (IBD) are characterized by an increased thrombembolic risk, given the powerful relation between inflammation and thrombosis. Multiple studies showed that patients with IBD have an up to 3-fold higher risk for developing venous thrombembolic (VTE) complications compared to general population, this risk being more increased in the hospitalized IBD flares. Thus, latest consensus recommendations indicate prophylaxis for VTE in hospitalized patients with active IBD but with no clear indications for the management of IBD outpatients. Regarding atherothrombotic risk (myocardial infarction or stroke), up-to-date data are inconclusive. IBD is associated with subclinical atherosclerosis in patients without clinical manifestations of cardiovascular diseases (CVD). However, the results of major studies assessing the hypothesis that IBD is strongly associated with atherosclerotic macrovascular events prove to be divergent even if they show positive correlations with CVD especially on different subgroup analysis. These facts should lead in the future to more prospective studies with control groups that have the same cardiovascular risk profile as in IBD populations in order to admit definitively that patients with IBD are exposed to an increased cardiovascular risk. Keywords: INFLAMMATORY BOWEL DISEASES, CARDIOVASCULAR RISK, VENOUS THROMBEMBOLISM, MYOCARDIAL INFARCTION, STROKE

Cardiovascular diseases (CVD) still represent the main cause of mortality worldwide despite the implementation of major programs of primary prevention. More than 70% of total deaths caused by CVD are determined by complications of atherosclerosis (about 50% - coronary disease, 20% - stroke).

Atherosclerosis represents a chronic inflammatory disease which is characterized by general inflammation. The immune mechanisms, in combination with well known metabolic risk factors (e.g. hypercholesterolemia, smoking), are key components in the initiation, activation, propagation and complication of the atherosclerotic plaque that, by rupture and thrombosis, will finally lead to acute coronary syndromes, strokes or other acute manifestations (1). In the last years, there is a growing interest in the involvement of the inflammatory and immune actions in the process of athero-
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genesis that will lead in the future to a translational medicine from the pathogenesis to clinical approaches of atherosclerosis. More biomarkers promise to play a great role in detecting subclinical activity, such as high-sensitivity C reactive protein (hs-CRP), cytokines (IL-6), proteases such as matrix metalloproteinase 9 or myeloperoxidase (2). The major problem is that in more than 30% of cases, the first clinical manifestation of atherosclerotic burden is a myocardial infarction. This is due to the fact that the disease acts undetected or the patient is wrong classified into a lower risk class with an inappropriate treatment and weak prevention measures.

Taking into consideration the upmentioned facts, it is with no doubt and it is well proved that chronic inflammatory diseases, such as systemic lupus erythematosus, rheumatoid arthritis or psoriasis, are associated with an increased cardiovascular risk. Regarding inflammatory bowel diseases (IBD), the relationship with atherothrombotic cardiovascular events is quite unclear, even if certain studies tend to suggest that there is a direct connection between these two diseases. Thus, our aim is to provide a concise overview over the current and latest studies regarding the relationship between inflammatory bowel diseases and the associated cardiovascular risk.

IBD include two main entities: Crohn’s disease and ulcerative colitis, with an estimated prevalence of 2.2 million persons in Europe. Even if it is long studied, the precise pathological mechanisms that lead to the development of the diseases are not fully understood. Certain contributing factors are represented by cigarette smoking, family history of IBD and appendectomy (3).

However, given the inflammatory status in IBD, these patients possess a greater thrombembolic risk, the link between thrombosis and inflammation being well recognized. This may be due to different mechanisms such as microvascular injury, a state of hypercoagulability, increased platelet activation or higher incidence of hyperhomocysteinemia in IBD patients (4, 5).

Moreover, in patients without clinical manifestations of CVD, IBD is associated with subclinical atherosclerosis, with increased carotid intima media thickness, arterial stiffness, hs-CRP, homeostasis model assessment of insulin resistance (HOMA-IR) or atherogenic lipid profile, suggesting higher risk of atherothrombotic disease (6).

There is a general agreement that patients with IBD have an increased risk of thrombembolic manifestations with the predominance of venous rather than arterial complications.

Multiple metaanalysis have proven that patients with IBD have an up to 3-fold higher risk for developing venous thrombembolic (VTE) complications compared to general population, this risk being even more increased in the hospitalized IBD patients (7, 8).

In a large case-control study involving almost 100,000 cases, Grainge et al. prove that patients with IBD had higher risks of VTE events, with an up to 8-fold higher risk during the IBD flares (9). In IBD inpatients, the prevalence of venous thrombembolism is 32% increased in patients with Crohn’s disease than in those with ulcerative colitis, but overall two times higher than in subjects without IBD. This fact leads finally to higher treatment charges and mortality in IBD patients that associate thrombotic complications (10). Another multicenter study concludes that patients
with IBD and venous thrombembolism are more prone to develop recurrent venous thrombembolism. But the same study states that it is uncertain which patients would benefit from prolonged therapy with anticoagulant, taking into the balance both the risk of bleeding and the risk of recurrent thrombotic complications (11).

However, current consensus recommendations indicate prophylaxis for venous thrombembolism in hospitalized patients with active IBD. Thrombophylaxis proves to be safe in patients with IBD even during a flare when there is rectal bleeding. Despite this evidence, up to two thirds of gastroenterologists do not administer venous thrombembolism prophylaxis to patients hospitalized with acute colitis. There is a great unevenness among physicians regarding the necessity, the way the VTE prophylaxis should be performed and the long term follow of such cardiovascular complications (12). Future clinical trials are needed to confirm safety and effectiveness of venous thrombembolism prophylaxis in patients with IBD. This last statement is underlined by other recently published studies which confirm that approximately half of thrombembolic events in IBD patients occur after hospital discharge, especially in those with additional risk factors for VTE (e.g. after a hospitalization for an IBD flare or after surgery) (14, 15). Moreover, IBD subjects present in the first 30 days after surgery a double risk for developing deep vein thrombosis or pulmonary embolism compared to general population, but without higher additional risk for myocardial infarction or stroke (16).

Taking into account these considerations, in 2014 is released the Canadian Association of Gastroenterology guidelines regarding treatment and prophylaxis of venous thrombembolism in patients with IBD which makes the following main recommendations based on current evidence (17). For:

- hospitalized IBD patients with moderate-severe IBD flares without severe bleeding, it is recommended anticoagulant thrombophylaxis with low molecular weight heparin, low-dose unfractionated heparin or fondaparinux;
- IBD patients, even in clinical remission, hospitalized for other medical indications unrelated to IBD, it is recommended anticoagulant thrombophylaxis;
- IBD patients that underwent major general or abdominal-pelvic surgery, it is recommended anticoagulant thrombophylaxis during hospitalization;
- outpatients with IBD flare who did not experience a previous venous thrombembolism, it is NOT recommended anticoagulant thrombophylaxis;
- IBD outpatients with a previous venous thrombembolism and are no longer on anticoagulation, it is recommended anticoagulant thrombophylaxis during moderate-severe IBD flares;
- IBD patients who undergo their first venous thrombembolism episode, even with IBD in clinical remission and in the absence of other provoking factor, it is recommended indefinite anticoagulant therapy with periodic reassessment of this indication;
- IBD patients with active disease, diagnosed with their first venous thrombembolism episode, it is recommended anticoagulant therapy at least until the IBD is in remission for 3 months or indefinite anticoagulant therapy.

Thereby, until new evidence regarding
anticoagulant treatment in IBD outpatients are released, an initial pragmatic approach is preferred in order to decrease the thrombembolic risk in IBD outpatients. This approach is represented, firstly, by an appropriate education of the patients for reducing and preventing thrombotic risk factors, recognizing early signs and symptoms of the venous thrombotic events and a regular clinical evaluation of the patients made by the specialist for the evaluation of possible venous complications (18).

While venous thrombembolic events have a higher incidence in subjects with IBD, the debate persists if IBD also correlates with atherotrombotic diseases including myocardial infarction or stroke.

A meta-analysis published in 2007, comprising 11 studies with more than 14000 participants concluded that IBD were not associated with increased CV mortality (19). In addition to this, Osterman at al. (20) conducted two retrospective cohort studies, with more than 25,000 patients with IBD with a mean follow-up of 4.5 years and found that neither Crohn’s disease nor ulcerative colitis had an increased risk of myocardial infarction. Another case-control study made by Ha et al. (21) supported once again the idea that these patients did not have an overall increased risk of arterial thrombotic events even if some subgroup analysis revealed some positive correlations (e.g. women below 40 years had a two-fold higher risk for stroke).

Nevertheless, there are studies that show direct causal link between IBD and further CV events. Bernstein et al. (22) concluded on more than 8,000 IBD patients that these subjects were more likely to develop cardiac atherosclerotic events, regardless of sex, with a 32% higher incidence of stroke in patients with Crohn’s disease. Moreover, in a cohort that included more than 8000 persons with Crohn’s disease, only the subgroup with younger patients (aged less than 50 years) presented a 3-fold increased risk of stroke but with no increased risk in older patients (23). Yarur et al. (24) proved in another 4-year cohort study that patients with IBD had a higher risk of coronary artery disease (hazard ratio 2.85) despite associating a lower burden of cardiovascular risk factors.

Probably the most important study that supports a direct causal link between CVD and IBD is the Danish Nationwide Cohort Study conducted by Kristensen (25) which included more than 20,000 patients with IBD matched for age and gender with 200,000 controls. The study concluded that there was an increased risk of myocardial infarction, stroke and CV death in patients with IBD but only during episodes of flare or periods of persistent active disease, whereas the risk was the same as in the control population in patients with IBD remission. However, this study did not take into consideration other cardiovascular risk factors or different treatments that the subjects could have followed at that time. One recently published evidence is offered by Singh et al. (26) in a systematic review over 9 studies. The authors found a slightly increased risk of stroke and ischemic heart disease in patients with IBD, especially in women, but with no difference for peripheral artery disease. The CVD risk was similar both for Crohn’s disease and for ulcerative colitis patients.

It is certain that IBD subjects are predisposed to an accelerated atherosclerosis process mostly secondary to chronic general inflammation. But with all the upmentioned inconsistent results, it is clear
there is a great heterogeneity in the population with IBD and with different degree of endothelial injury that finally leads to different CV risk. However, there are some categories that can be included into a higher risk, such as patients with extensive bowel involvement, longer activity or severe persistent disease (27).

In summary, IBD proves to be associated with an up to 3-fold increased risk of developing venous thrombembolic events. This leads to firm indication for anticoagulant thromboprophylaxis for IBD hospitalized patients. Regarding the atherothrombotic risk, there is good evidence that IBD have relevant subclinical atherosclerotic lesions. However, studies are divergent in concluding that IBD are strongly associated with macrovascular events, such as myocardial infarction or stroke, even if they prove positive correlations with CVD especially on subgroup analysis. There are needed more prospective studies with control groups that have the same cardiovascular risk profile as in IBD populations in order to conclude definitively that patients with IBD have an increased risk for developing CVD.

REFERENCES

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