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Cardiovascular risk in patients with inflammatory bowel diseases: a review

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Abstract

Patients with inflammatory bowel diseases (IBD) have an increased risk of cardiovascular events (myocardial infarction, cerebrovascular events and death of cardiovascular causes), because of some common pathophysiological mechanisms. Patients with IBD have high levels of cytokines, C-reactive protein and homocysteine, leading to endothelial dysfunction and atherosclerosis. Also, the increased levels of coagulation factors in patients with IBD lead to an increased risk for thromboembolic events. There are numerous studies that sustain the link between IBD and cardiovascular complications.

Keywords: inflammatory bowel diseases, cardiovascular events, thromboembolic events, atherosclerosis.

Introduction

Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gastrointestinal tract. The term inflammatory bowel diseases includes mainly the ulcerative colitis (UC) and Crohn's disease (CD). CD affects the mouth, esophagus, stomach, small and large intestine and the anus. UC affects mainly the large intestine and the rectum. IBD have an increasing incidence and prevalence, 1.4 milion people in the United States being diagnosed with IBD, while 2.2 milion persons in Europe suffer from IBD (HANAUER & al [1]). IBD have low incidence in Asia and in Southern Europe (YE& al [2]). A high incidence of IBD is in the northern areas, such as northern Europe and North America (BURISCH & al [3]). IBD occur more frequent in Caucasian people (NG & al [4]). UC is more frequent in men, while CD is more common in women (HANAUER & al [1]).

The etiology of IBD is poorly understood. Smoking, microorganisms, medication, diet and stress, but also genetic factors, enviromental and immunoregulatory factors are incriminated in the etiology and pathogenesis of IBD (YE& al [2]). The current hypothesis for the etiology of IBD is the genetic predisposition for immune dysregulation of the

gastrointestinal system.

IBD are associated with an increased risk for developing cardiovascular diseases (CVD) (NG & al [4]). Both entities have pathophysiological mechanisms that influence each other. Studies suggest that patients with IBD have an increased risk for developing myocardial infarction and stroke (FILIMON & al [5]). In a meta-review, Singh et al revealed that patients diagnosed with IBD are at increased risk of ischemic vascular diseases (SINGH & al [6]). In addition, this subgroup of patients are at high risk of developing cardiovascular events in the perioperative period, and they are in need for a specific management, especially during surgery (CHECHERITA & al [7]; (TIGLIS & al [8]).

Pathophysiological links between IBD and cardiovascular diseases

IBD are associated with high levels of cytokines, which are the inflammatory mediators that play an important role in the atherosclerotic process (HINGORANI & al [9]). C-reactive protein (CRP), a specific marker of inflammation, has high levels in the serum of the patients with IBD (SCHINZARI & al [10]). Studies suggest that CRP is associated with atherosclerosis and predicts mot only the risk of developing cardiovascular events (CHECHERITA & al [11]), but also kidney disease and the afferent complications (RIDKER & al [12]), joint and skin inflammation and uveitis. CRP is a marker of an increased risk for coronary heart disease and myocardial ischaemia, being associated with the atherosclerotic process (PRADHAN & al [13]).

The tumor necrosis factor alpha (TNF-alpha) is also an inflammatory mediator, which is found at high levels in patients with IBD. It has been demonstrated that TNF-alpha is a proatherogenic cytokine (SPRAGUE & al [14]). Studies noticed that inhibition of the TNF-alpha with infliximab is associated with improved endothelial function in patients with CD (SCHINZARI & al [10]).

The vascular endothelial growth factor (VEGF) and the interleukin-6 (IL-6) are proinflammatory mediators at high levels in the serum of patients with IBD. These mediators are involved in the atherosclerotic process through endothelial dysfunction (TESTA & al [15]).

IBD evoluate with endothelial dysfunction, which leads to atherosclerosis. In patients with UC, the degree of endothelial dysfunction is correlated with the severity of the disease (KOCAMAN & al [16]). In patient with advanced disease and associated comorbidities, it can complicate, for example, the vascular access and delayed the treatment (CHECHERITA & al [17]). A study on endothelial dysfunction in patients with IBD, conducted by Roifman et al, found that IBD are associated with microvascular dysfunction in both CD and UC (ROIFMAN & al [18]).

The intimal-media thickening (IMT) of the carotid arteries is a well-known marker of atherosclerosis. Van Leuven et al confirmed that a chronic inflammatory status is a risk factor for accelerated atherogenesis. In their study, conducted on 60 patients diagnosed with CD, they found that carotid IMT is increased in patients with IBD, compared with individuals from the control group, indicating accelerated atherogenesis (VAN LEUVEN & al [19]).

IBD are chronic inflammatory diseases, associated with disruption of the intestinal barrier. Concomitant gastrointestinal complications could develop and its can disturb furthermore the digestive tract. As a result, microbial products, lipopolysaccharide (LPS) and endotoxins pass the intestinal mucosa and enter into the bloodstream. LPS contributes to

atherosclerosis by activation of the macrophages, accelerating atherosclerosis (HOWELL & al [20]). Also, LPS stimulates the oxidation of the LDL-cholesterol, contributing to endothelial dysfunction (WIEDERMANN & al [21]).

The effects of the microbial products on the atherogenesis in IBD is mediated by Toll-like receptors (TLR2) and TLR4. These receptors are, also, at increased levels in the atherosclerotic plaque (EDFELDT & al [22]). Studies on this issue suggest that TLR2 and TLR4 could be a link between IBD and cardiovascular diseases (KIECHL & al [23]). Other studies did not offer conclusive results regarding the implications of TLR as a marker of atherosclerosis in IBD. A recent study showed that treatment with antibiotics in IBD is associated with a decreased incidence of myocardial infarction(LAM & al [24]).

The patients diagnosed with IBD have altered lipid profiles, being at high risk for atherosclerosis. The high levels of inflammatory cytokines in IBD alters the degradation of the lipids (ANDERSON & al [25]). A retrospective review on the patients with IBD, conducted between 2000 and 2007, noticed that patients with IBD have low levels of HDL-cholesterol and high levels of LDL-cholesterol (SAPPATI BIYYANI & al [26]). The decreased levels of HDL-C may confer an increased risk of developing coronary artery disease. Data from epidemiological studies have shown that a pro-inflammatory state changes the function of the HDL-C (LAM & al [24]). Some authors showed that chronic inflammation in IBD leads to alterations in the lipids, apolipoprotein and lipoprotein profile (KHERA & al [27]). A study conducted by Ridker regarding the use of statins for the prevention of vascular events, noticed that statin-therapy reduces CRP levels, inhibiting atherogenesis (RIDKER & al [12])

IBD are associated with abnormalities of the coagulation system, such as hypercoagulability (SCALDAFERRI & al [28]). A recent comprehensive review on this issue highlighted the mechanism of hypercoagulability in patients with IBD: the high levels of coagulation factors and thrombin and fibrin formation products, vascular endothelial deficiencies and elevated levels of circulating platelets (ZEZOS & al [29]). Also, patients with IBD have a decreased ability of fibrinolysis and are at high risk of thromboembolism, because they have increased levels of activated circulating platelets, with tendency to create platelet aggregates (PRINCIPI & al [30]). It was demonstrated that UC is a disease associated with a hypercoagulable state (KUME & al [31]). In a study by Vegh et al, conducted on 1708 patients diagnosed with IBD, followed for 35 years, it was noticed that the risk for venous thromboembolism was 1.03 per 1000 patients-year (VEGH & al [32]). IBD are associated with an increased expression of CD40, which induces endothelial inflammation, an important process in the atherosclerosis development (GRIFFITHS & al [33]).

The patients with IBD have an increased serum levels of homocysteine, a product generated from the methionine metabolism (DRZEKOWSKI & al [34]). A study conducted by Kanani et al regarding the role of the oxidative stress in the endothelial dysfunction, noticed that increased homocysteinemia leads to endothelial dysfunction (KANANI & al [35]). Homocysteine generates products of oxidative stress, inhibiting the vasodilator effects of the nitric oxide and stimulating the release of inflammatory cytokines, resulting in endothelial dysfunction (MCCULLY & al [36]). So, homocysteine has an important role in the process of atherosclerosis.

The cardiovascular system involvement in IBD

IBD are hypercoagulable and proinflammatory diseases, being associated with thrombotic

vascular events. A Danish nationwide cohort study, which enrolled 20.795 patients with IBD, for a mean period of 6 years, reported that IBD are associated with an increased risk of myocardial infarction and death from cardiovascular causes (KRISTENSEN & al [37]). This cohort showed that the risk of myocardial infarction, stroke and cardiovascular death is increased in patients with IBD, especially in the periods when the disease is active. In a cohort study from the UK, which included 8000 patients with CD, it was observed that IBD are associated with an increased risk of stroke, especially in young patients (<50 years) (ZEZOS & al [29]).

IBD are associated with coagulation anomalies, with high levels of circulating coagulation factors, with an increased tendency for hypercoagulation. Patients with IBD are at increased risk of developing thromboembolic events, such as pulmonary thromboembolism, arterial occlusive disease, superior vena cava and mesenteric thrombosis, arteritis and deep vein thrombosis. In a meta-analysis, which included 33 studies, conducted on 207,814 patients with IBD, it was reported that IBD are associated with an increased risk for venous thromboembolism (FUMERY & al [38]). In a recent study, which evaluated global coagulation profiles in patients with IBD, it was demonstrated that UC is a hypercoagulable disease (VEGH & al [32]).

A large retrospective study regarding the venous thromboembolic complications in patients with IBD, conducted on 7199 patients, reported that 1.3% of these patients developed thromboembolic complications, including deep vein thrombosis and pulmonary embolism with high rate mortality. 77% of all thrombotic pulmonary events occured spontaneously (DAVI & al [39]).

Also, it was reported that IBD are associated with peripheral artery thrombosis, coronary thrombosis and mesenteric and portal vein thrombosis. Studies on this pathological association showed that arterial occlusive disease is most frequent in patients with cardiovascular risk factors receiving steroid therapy (YARUR & al [40]). There are studies that also confirm the fact that in the active phase of the disease, and due to the corticosteroid therapy, the patients are at risk of developing bone fractures on the back of reduced bone mass, especially in patients with associated diabetes or renal disease, and they need a specific surgical management (NEAGU & al [41]; POIANA & al [42]; DAVID & al [43]).

A large study, which assesed the risk of pulmonary embolism in patients with IBD, conducted on 55.496 subjects, observed an increased risk for pulmonary embolism in IBD, compared to the general population (BERNSTEIN & al [44]). Also, left ventricle and right atrium thrombosis have been reported in patients with UC, due to the infective endocarditis (YARUR & al [40]).

The coronary arteries present changes in patients with IBD, due to atherosclerosis, with rupture of the atherosclerotic plaque and thrombosis, resulting in myocardial ischaemia and acute myocardial infarction, especially when cardiovascular risk factors are associated (smoking, dyslipidemia, family history of coronary artery disease, diabetes, hypertension) (CAPATANA & al [45]; COCOLOS & al [46]; HA & al [47]). C-reactive protein and interleukin-6, which are increased in patients with IBD, especially in the IBD flares, are associated with an increased risk of coronary heart disease and mesenteric ischemia (AGGARRWAL & al [48]). A canadian study of 8000 IBD patients revealed an increased risk of ischaemic heart disease in these patients (FUMERY & al [38]). Studies showed that patients with IBD are diagnosed with coronary artery disease at a younger age, compared with the general population (NECHITA & al [49]). Over the time, patients with

inflammatory bowel disease can develop cardiac insufficiency, thus aggravating the general manangement (KRISTENSEN & al [50]). The cohort studies, which assessed the association of IBD with the risk of cerebral and heart ischemia, reported cases of stroke and myocardial infarction in patients with IBD. These studies observed that the presence of IBD is associated with an increased risk for developing ischemic heart disease (& al [6]). Also, the Danish cohort study observed that IBD are associated with increased hospitalization for heart failure (& al [5]).

IBD are also associated with endocardial, pericardial and myocardial complications. Infective endocarditis is a severe complication in patients with IBD, that occurs especially in patients with central venous catheters, endocardial abnormalities or in those with bacteriemia, as a result of immunosuppresion. Enterococcus faecium and streptococus bovis are the most frequent microorganisms involved in these cases (SINGH & al [51]). A single case of right atrium abscess with staphyloccocus has been reported in a patient with IBD and with prolonged central venous access (KATSANOS & al [52]). Endocardial involvement is a severe complication in IBD (QUERCIA & al [53]).

Myocarditis is a rare complication of IBD. It is more frequent in patients with UC (GRIFFITHS & al [33]). When it appears, it is associated with pericarditis (myopericarditis). The Danish cohort study described 6 cases of patients with IBD, diagnosed with myocarditis (KRISTENSEN & al [37]). A frequent cause for myocardial involvement in patients with UC is prolonged therapy with mesalamine. Also, in patients with CD, myocardial complications are due to the selenium deficiency. The patients with central venous catheters, accusing palpitations, precordial pain and arrhythmias should be suspected for myocarditis (HITOSUGI & al [54]). In the literature, it was described a case of sudden death in a 29-year-old man with CD, due to atrophic changes of the myocardium (GREENWOOD & al [55]).

Pericarditis is the most frequent cardiac complication in IBD. Pericardium is involved in IBD as an extraintestinal manifestation of the intestinal disease or as a side effect of the therapy. Pericarditis in IBD can be induced by the therapy with azathioprine, mesalamine or with cyclosporin-A (QUERCIA & al [53]). In the literature, it has been reported a case of pericarditis due to infection in a patient with pericardio-colonic fistula (GREENWOOD & al [55]). Pleuropericarditis is a rare complication in IBD, frequently being associated with vasculitis and arthritis. Pericardial tamponade is a rare complication in patients with IBD, but when appears, it needs urgent therapy (KATSANOS & al [52]).

Also, patients with IBD may present heart rhythm disorders and conduction disorders, such as atrial fibrillation and ventricular tachyarrythmia, sinusal bradicardia (due to mesalamine therapy) and atrio-ventricular block (QUERCIA & al [53]).

Heart valve complications are seen in patients with IBD, as a result of other cardiac complications, such as endocarditis. In patients with CD, the most frequent valvular complication is aortic regurgitation (WECKERLIN & al [56]). Also, CD is associated with tricuspid valve involvement in fungal endocarditis. In some cases, surgical valve replacement is needed (KATSANOS & al [52]).

Acute heart failure was reported in patients with IBD and acute myocardial infarction, myocarditis, pericardial tamponade and cardiac valve complications (DAGLI & al [57]).

Therapeutical agents used in IBD and the cardiovascular risk

Some agents used for the treatment of IBD may have beneficial protective effects against ischaemic heart disease, reducing the cardiovascular risk. The analgesic therapy should be

take into account in order to avoid further complications.

TNF-alfa antagonists are used in the treatment of patients with IBD, reducing the inflammatory status and healing the intestinal mucosa. Their anti-inflammatory role in reducing the cardiovascular risk in IBD is limited. In a cohort study in Denmark, on 50.756 patients with IBD, it was revealed that the patients who were not treated with TNF-alfa antagonists, developed more frequently ischaemic heart disease[5]. These data suggest that TNF-alfa antagonists have a protective effect, but further studies are necessary to confirm this effect (CROCKETT & al [58]). The Danish cohort study found no cardiovascular events in patients treated with TNF-alfa inhibitors during the period of the study. In the same study, 6017 patients were treated with azathioprine, 6-mercaptopurine and methotrexate, with similar cardiovascular risk as the total IBD subjects in the study (KRISTENSEN & al [37]).

Salicylates could have beneficial effects in reducing the cardiovascular risk. The longitudinal studies observed that salicylates therapy in patients with IBD is associated with an increased carotid-femoral pulse wave velocity at follow-up. The same studies revealed that steroids, azathioprine or anti-TNF alfa are not associated with this effect (ZANOLI & al [59]).

Statins have a beneficial effect on decreasing the process of atherosclerosis, but in patients with IBD their role is still uncertain. Further studies are needed to clarify their potential (ZANOLI & al [59]). It is important to reduce the cardiovascular risk in this subgroup of patients, especially in those with renal failure, where the cardiovascular comorbidities and gastrointestinal disorders are frequent (LEBLEBICIOGLU & al [60]).

Therapy with steroids in patients with IBD is associated with hypertension, myocardium atrophy, increased risk for congestive heart failure (WALKER & al [61]). Also, corticosteroids could have prothrombotic effects (KRISTENSEN & al [37]). It should be take into account that this therapy can complicate the evolution of patients with neoplastic associated disease (NEAGU & al [62]; POIANA & al [63]; NEAGU & al [64]).

Treatment with mesalamine or mesalazine is associated with myocarditis or perimyocarditis, pericarditis and sinusal bradycardia. Also, azathioprine could affect the pericardium, leading to pericarditis (SCHICO & al [65]).

Conclusions

IBD are proinflammatory and hypercoagulable diseases, being associated with coronary artery disease with myocardial infarction and cerebrovascular events. There are numerous evidences that IBD are associated with increased cardiovascular risk. Studies revealed that treatment used in IBD for the disease remission, may reduce cardiovascular risk. Further studies are needed to clarify this issue.

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