

## **Inflammation and Endothelial Dysfunction Common Mechanisms of Inflammatory Bowel Diseases and Cardiovascular Disease**

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### **Abstract**

Chronic inflammatory bowel diseases (IBD) - essentially comprised of Crohn's disease (CD) and ulcerative colitis (UC) - are a major health problem worldwide with increasing incidence. Although CD and UC are characterized by, clinically different characteristics, both diseases lead to a chronically remitting inflammatory process of the gastrointestinal tract, as well as possible extra-intestinal manifestations. One of the extra-intestinal manifestations is cardiovascular forms of clinical presentation. According to the existing data, both groups of diseases shares common molecular, pathomorphological and pathophysiological changes. The most common cardiovascular manifestations as described are: ischemic heart disease, cerebrovascular disease, Takayasu's arteritis, pericarditis and myocarditis and venous thromboembolism. The diagnostic approach for CVD in patients with IBD is not different from general population. However, considering the effects of different IBD treatment options on cardiovascular presentations, there is not enough evidence to support or dismiss its beneficial effects, given the fact that there is some evidence that IBD medications can even worsen the underlying pathomorphological and pathophysiological changes and clinical presentation of CVD.

**Keywords:** *Chronic Inflammatory Bowel Disease; Cardiovascular Disease; Endothelial Dysfunction; Atherosclerosis*

### **Introduction**

Inflammatory bowel diseases (IBD) - essentially comprised of Crohn's disease (CD) and ulcerative colitis (UC) - are a major health problem worldwide with increasing incidence. Although CD and UC are characterized by, clinically different, characteristics, both diseases lead to a chronically remitting inflammatory process of the gastrointestinal tract, as well as possible extra-intestinal manifestations.

### **Chronic inflammatory bowel diseases pathogenesis**

Inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, have a multifactorial etiology. IBD patients have a genetic predisposition to pathological interactions between the intestinal microflora and the immune system. Once the inflammatory process starts, every disbalance between the regulatory and inflammatory cytokines leads to its prolongation. Endothelial dysfunction also plays an important role in the pathogenesis of IBD, leading to chronic micro vessel inflammation, originally by increasing the production of cell adhesion molecules (CAMs) (selectins, integrins and immunoglobulins), leading to an enhanced leukocyte adherence capacity, as compared to healthy control vessels. IBD patients present with an upregulated microvascular expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Vowinkel, *et al.* demonstrated a significant increase in endothelial CD40 expression, resulting in increased leukocyte recruitment [2].

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Damen, *et al.* introduced interleukin-32 (IL-32) as another inflammatory cytokine to play an important role in the IBD inflammation process. The IL-32 $\epsilon$  isoform has been identified in human colonic subepithelial myofibroblasts (SEMFs). IL-32 expression can be induced by muramyl dipeptide (MDP), a bacterial peptidoglycan fragment, and a potent nucleotide binding oligomerization domain containing 2 (NOD2) ligand, resulting in increased IL-6 and IL-1 $\beta$  production. IL-32 is thought to have an important role in the pathophysiology and progression of Crohn's disease. IL-32 $\epsilon$  correlates with TNF- $\alpha$  levels and reduces the TNF- $\alpha$ -induced IL-8 transcription. There is a wide variation of the effects of different IL-32 isoforms on IBD pathophysiology and progression [3].

IBD patients also present with reduced nitric oxide (NO) production, probably caused by increased arginase activity (an enzyme that competes with nitric oxide synthase (NOS)). The vascular endothelium is also targeted by TNF- $\alpha$ . TNF- $\alpha$  - TNF-receptor binding reduces endothelial NOS (eNOS) protein expression and suppresses eNOS activity, indirectly diminishing the degradation of asymmetric dimethylarginine (ADMA), an endogenous eNOS inhibitor [2].

Reactive oxygen species (ROS) are also produced in the inflamed area, generating oxidative stress in Von Willebrand Factor (vWF) molecules, inhibiting cleavage of vWF molecules and creation of ultra-large vWF multimers, all resulting in microvascular thrombosis in IBD patients [2].

Besides endothelial dysfunction, IBD is characterized by structural changes in the vascular endothelium, leading to capillary and venule remodeling, and endothelial cell proliferation. Angiogenesis is a crucial process that sustains chronic inflammation in the gastrointestinal tract (GIT). Various inflammatory cell types, including macrophages, lymphocytes, mast cells, and fibroblasts, produce angiogenic factors and promote angiogenesis. The hypoxia in the inflamed area also stimulates angiogenesis through vascular endothelial growth factor (VEGF), fibroblast growth factor, and TNF- $\alpha$  upregulation. Rutella, *et al.* suggested that the previous results in platelet recruitment, increased production of pro-angiogenic VEGF-A and CD40 ligand (CD40L) [2].

### Diagnostic methods for endothelial dysfunction detection in patients with inflammatory bowel disease

Endothelial dysfunction can be assessed by physical and biochemical methods.

Physical methods are based on measuring vasodilation in large arteries in response to increased flow and receptor stimulation, mainly using acetylcholine, with flow-mediated vasodilation (FMD) being the most sensitive and widely used diagnostic measure. However, these methods do not accurately reflect endothelial function in the microcirculation and are less sensitive for detecting early endothelial function changes. On the other side, biochemical methods are based on assessing the synthesis of compounds produced by normal and damaged endothelium, given the fact that abnormal endothelium releases several specific compounds. Authors such as Kocaman, Roifman, Theocharidou, Aloi, Zanoli, and their respective co-authors, have demonstrated endothelial dysfunction by applying different physical and biochemical methods (pulse arterial tonometry, carotid intima-media thickness, flow-mediated vasodilatation, arterial stiffness, carotid-radial pulse wave velocity (PWV), etc.) [2].

Fewer studies have measured serum endothelial dysfunction biomarker levels in IBD patients. Adamska, *et al.* reported a significant increase in E-selectin expression in patients with active CD, compared to patients in remission. Similarly, Goggins, *et al.* demonstrated increased levels of ICAM-1 and E-selectin in IBD patients. Magro, *et al.* showed that P-selectin, E-selectin, VCAM, ICAM, VEGF, and angiogenin serum levels are significantly lower in patients with inactive CD, compared with controls, suggesting a dysfunction in the angiogenic process and wound repair. Inactive IBD patients have shown lower VEGF and angiogenin levels compared to patients presenting with an active disease [2].

### Inflammatory bowel diseases, the risk of cardiovascular disease and cardiovascular manifestations

IBD is an established risk factor for cardiovascular disease (CVD). Patients with IBD were shown to have a twofold to threefold increased risk for venous thromboembolism, especially during acute disease phases, which present with disturbed homeostasis of anti- and

procoagulants, leading to a hypofibrinolytic state. Ischemic heart disease, cerebrovascular disease, Takayasu's arteritis, pericarditis and myocarditis, are also described in patients with CD and UC, but without increased CV mortality [1,4]. On the other side, a population-based study from Denmark and a nationwide register from Finland, have both shown increased cardiovascular mortality in IBD during periods of active inflammation, and also showed that patients with UC, but not CD, have increased CVD mortality (RR 1.14 [95% CI, 1.06 - 1.22]) [4].

Female patients are primarily associated with an increased risk of cerebrovascular accident (OR 1.28 [95% CI, 1.17 - 1.41]) and ischemic heart disease (OR 1.26 [95% CI, 1.18 - 1.35]) and the risk of cerebrovascular accident is higher in young IBD patients [< 40 - 50 years old]. Approximately 1/10 000 patients admitted to a hospital presents with mesenteric ischemia, with a pooled risk ratio of 3.46 [95% CI, 1.78 - 6.71]. The rate of peripheral vascular disease is low in IBD, affecting only 0.5% of patients [4].

The chronic persistent/remittent inflammation exposure and altered lipid metabolism are thought to be the major contributors to CV pathology, even though they are also considered as adverse effects of long-term anti-inflammatory drug administration (corticosteroids, TNF- $\alpha$  inhibitors, etc.). Studies in adult and pediatric patients have demonstrated an association of IBD and early signs of subclinical atherosclerosis [3,4]. Atherosclerosis in IBD patients occurs due to a combination of inflammation, endothelial dysfunction, calcification, and hypercoagulability, increased accumulation of oxidized low-density lipoproteins (LDL), leukocytes, and smooth muscle cells in the intima of the artery, with inflammatory cytokine release (TNF- $\alpha$ , IL-6, C-C motive chemokine ligand 2 (CCL-2)), resulting in atheroma development and expansion. Hyperhomocysteinaemia, a risk factor for arterial and venous thrombosis, is four times more prevalent in IBD patients, compared to the general population [4].

The low prevalence of cardiovascular risk factors [hypertension, diabetes, dyslipidemia, obesity, or the composite Framingham risk score] in IBD patients, can underestimate the risk of CVD in IBD patients who have chronic systemic inflammation, leading to premature atherosclerosis [1]. Fan., *et al.* considers the traditional risk factors as a major predictor of arterial stiffness in IBD patients, as opposite to Ozturk., *et al.* which suggested that patients with IBD without traditional cardiovascular risk factors have higher risks for endothelial dysfunction and atherosclerosis. More clinical evidence is needed in order to draw a conclusion [2].

Clinical features, investigations and diagnostic criteria of cardiovascular events are similar in patients with and without IBD [4]. Doppler-based ultrasound studies have been utilized to reveal both increased arterial stiffness and carotid intima-media-thickness (IMT) in adult patients with CU. Speckle tracking echocardiography (STE) has been used to identify early subclinical cardiac involvement, as it is a sensitive method that can detect discretely altered myocardial contractility due to transient changes in serum glucose levels [1].

### Pharmacological interventions in IBD and CVD effects

There is growing evidence stating that IBD treatment can reduce cardiovascular risk by suppressing inflammatory activity. Recently published, Danish, population-based studies analyzed the effect of IBD therapy on cardiovascular complications. They reported a lower rate of ischemic heart disease in patients treated with 5-aminosalicylic acid (RR 1.16 [95% CI, 1.06 - 1.26]) as compared to non-treated patients (RR 1.36 [95% CI, 1.22 - 1.51]); similar results were reported for ischemic heart disease (IHD) and treatment with thiopurines and TNF- $\alpha$  antagonists. Treatment with anti-TNF- $\alpha$  agents was also reported to lead to lower rates of myocardial infarction, cerebrovascular accident, and cardiovascular death. Patients should be advised to avoid known cardiovascular risk factors, including cigarette smoking [4].

Santos., *et al.* demonstrated the inverse mechanisms by which patients with UC in clinical remission are at higher CVD risk. In IBD patients, UC specifically, clinical remission results in adipose tissue changes, such as: increased body fat, reduced fat-free mass, increased BMI and waist circumference, diabetes mellitus and dyslipidemia. These changes are related to poor eating habits, physical inactivity, and

previous use of steroids, leading to increased number of adipocytes, reduced volume and increased inflammatory infiltrate of mononuclear cells, and expanded inflammatory capacity [5]. The amino salicylates + azathioprine treatment reduces inflammation and increases anti-inflammatory cytokines, leading to better regulation of the inflammatory processes and reducing the risk of CVD [5].

Other pharmacologic agents found to be effective in IBD are those directed against TNF- $\alpha$ -mediated inflammation, such as infliximab infusion. Arijs, *et al.* showed that these drugs lead to disappearance of the inflammatory cells from the intestinal lamina propria and restoration of the cell adhesion molecules. There are reports suggesting that anti-TNF- $\alpha$  antibodies inhibit angiogenesis in patients with IBD. The effects of TNF- $\alpha$  on the cardiovascular system could be beneficial and harmful at the same time, due to concentration-related differences in different receptor activation. Regarding corticosteroid treatment, no effects on endothelial function have been reported [2].

Cyclosporine leads to increased endothelial cell activation, as found in various “in vitro” studies. However, there are also studies suggesting that cyclosporine A inhibits angiogenesis targeting VEGF-A, while azathioprine (and its metabolite, 6-mercaptopurine) has a protective role against the activation of endothelial cells [2].

New treatment options for IBD patients include anti-adhesion molecules, such as vedolizumab and etrolizumab. Vedolizumab targets  $\alpha 4$ - $\beta 7$  integrins, and blocks interactions between  $\alpha 4$ - $\beta 7$  integrins and MAdCAM-1. Etrolizumab targets the  $\beta 7$  subunit, and PF-00547659 is a monoclonal antibody against MAdCAM-1. Others, such as laquinimod and tofacitinib, reduce the synthesis of pro-inflammatory cytokines [2].

### Conclusion

There is enough evidence supporting the theory that inflammatory bowel diseases share similar, if not the same, pathophysiological mechanisms as cardiovascular disease. Cardiovascular involvement is one of the extraintestinal presentations of IBD.

However, considering the effects of different IBD treatment options on cardiovascular presentations, there is not enough evidence to support or dismiss its beneficial effects, given the fact that there is some evidence that IBD medications can even worsen the underlying pathomorphological and pathophysiological changes and clinical presentation of CVD.

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