Journal of Surgery
[Jurnalul de Chirurgie]

Review open access

The development of atherosclerotic cardiovascular disease in inflammatory bowel disease

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Abstract:
Inflammatory bowel disease (IBD) is a group of disorders that are characterized by chronic inflammation. The prevalence and incidence of inflammatory bowel disease have increased in time. Many studies have demonstrated that chronic inflammatory conditions are associated with atherosclerosis and cardiovascular events. The purpose of this extensive literature review is to present systemically the latest data on the epidemiology, risk factors and common pathophysiology of the two diseases, the effects of IBD treatment, as well as the influence of intestinal microbiota, vitamin D, but also dietary patterns in ASCVD and IBD. The intestinal microbiota can increase the risk of cardiovascular disease in IBD by deteriorating intercellular connections. Endotoxins, especially lipopolysaccharides, from the intestine can enter the circulatory system and can intensify the process of atherogenesis by chronic systemic inflammation.
Further studies are needed to identify risk factors in the early stages so as to assess risk stratification and optimal treatment.

Keywords: atherosclerotic cardiovascular disease, inflammatory bowel disease, ulcerative colitis, Crohn's disease, chronic inflammation.

Introduction

Inflammatory bowel disease (IBD) is a chronic, systemic inflammatory condition affecting the gastrointestinal tract and includes the following clinical entities: ulcerative colitis (UC) and Crohn's disease (CD) (1). For a long time, inflammation has been recognized as a key factor in the pathogenesis of atherosclerotic cardiovascular disease (ASCVD), as well as proinflammatory markers responsible for the development of coronary artery disease (2).

The process of atherosclerosis is characterized by inflammation in the arterial wall and systemically in the body, thus causing increased levels of C-reactive protein (3,4,5). Several non-specific mechanisms are involved, such as the release of cytokines and mediators (TNFα factor, interleukin 1) and platelet activating factors causing the loss of

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Received: June 01, 2021; **Accepted: September** 30, 2021**; Published: December** 23, 2021
Citation: Seritean Isac Petronela Nicoleta, Popescu Diana, Genes T. M., Ouatu Anca, Badescu Minerva Codruța, Tanase Daniela Maria, Dima Nicoleta, Rezus Ioana Irina, Rezus C.: The development of atherosclerotic cardiovascular disease in inflammatory bowel disease. Journal of Surgery [Jurnalul de chirurgie]. 2021; 17(4): 241 – 249, DOI: 10.7438/JSURG.2021.04.03

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hemostatic balance to a prothrombotic state (3).

IBD also has inadequate immuno-inflammatory activity and the pathophysiology of inflammation of the intestinal wall shares common features with processes in the arterial wall, from the progression of atherosclerosis to rupture of atherosclerotic plaque and thrombosis (6,7).

The purpose of this extensive literature review is to present systemically the latest data on the epidemiology, risk factors and common pathophysiology of the two diseases, the effects of IBD treatment, as well as the influence of intestinal microbiota, vitamin D, but also dietary patterns in ASCVD and IBD.

Epidemiology

The incidence of atherosclerotic cardiovascular disease in patients with IBD is increased as reported in recent studies (8). Data published by the Danish cohort study have an increased risk of myocardial infarction (MI) - risk ratio (RR) 1.17, stroke (stroke) - RR 1.15 and cardiovascular mortality - RR 1.17, especially during periods of disease activity, increasing in MI to RR- 2.05, in stroke to RR -1.55 and in cardiovascular mortality up to RR- 2.50. This increased risk dependent on IBD activity suggests that systemic inflammation contributes to the pathophysiological mechanisms that cause atherosclerosis (9).

Another Canadian cohort study of patients with IBD in which traditional and nontraditional risk factors were evaluated showed that despite the fact that they have a lower burden of traditional risk factors, the incidence of coronary events was increased. (HR (Hazard Ratio) -2.85). Regarding the risk factors for the development of coronary heart disease, the number of leukocytes was a risk factor for the development of coronary heart disease (HR 1.23) (10). Recently, a meta-analysis of 11 studies, reported an RR-1.17 for coronary heart disease, RR -1.12 for MI and RR -1.25 for cerebrovascular disease (11). Regarding cardiovascular mortality, an extensive meta-analysis published in 2013, which included 35 studies, enrolling 32,269 patients with CD and 18,952 patients with UC, concluded that the mortality rate was not increased for either UC or CD (12). Another extensive meta-analysis published by Furmery et al. in 2014, which enrolled 207,814 patients with IBD and 5,774,898 control patients, it concluded that there is also an insignificant risk of cardiovascular mortality compared to the general population (13).

The risk of ASCVD in patients with IBD is not associated with an increased prevalence of traditional risk factors. A recent study showed that there is no increase in traditional risk factors in patients with IBD. Thus, patients with IBD had lower values of blood pressure, total cholesterol and LDL cholesterol levels compared to the general population. The other traditional risk factors represented by plasma glucose and body mass index, showed comparable results in IBD and the general population (14).

Regarding risk factors for ASCVD in patients with IBD, the relative risk of ischemic heart and cerebrovascular disease is

higher in female and 40-year-old patients, respectively (1).

Common physiopathology of the two diseases

Atherosclerosis is the most common cause of ischemic heart disease and cardiovascular disease. In both atherosclerosis and IBD, chronic inflammation is present along with endothelial and platelet dysfunction. Endothelial cells, lymphocytes, monocytes, macrophages and smooth muscle cells are involved in the pathogenesis of atherosclerosis, from foaming to plaque development (8,15). Disruption of the endothelium in the process of atherosclerosis will cause the deposition of subendothelial lipoproteins and the recruitment of monocytes from the spleen and bone marrow. Adhesion molecules such as VCAM1, P-selectin and ICAM-1 will determine the expression of chemokines CC1, CCR5 and CX3C receptor (16,17,18).

As some of these adhesion molecules are also involved in the pathogenesis of IBD, they are also considered a possible drug therapeutic target. Vedolizumab is a humanized monoclonal antibody, widely used in the treatment of CD and UC, which prevents the recruitment of leukocytes in the intestine by inhibiting the binding of adhesion molecules on the surface of monocytes (8,19).

To demonstrate the role of endothelial dysfunction in patients with IBD, a team of researchers evaluated the dilation of intestinal micro vessels mediated by nitric oxide (NO), concluding that in IBD chronically inflamed micro vessels rely on cyclooxygenase-dependent vasodilating mechanisms in parallel with loss of dependent response. of NO (20).

The pathogenesis of atherosclerosis also involved in the adaptive immune system represented by dendritic cells and B lymphocytes. Activation of helper T cells (Th1) will cause the production of proinflammatory cytokines (IL-1, IL-6, TNF-α) that will activate the inflammatory cascade. Thus, cytokines play a dual role in the process of atherosclerosis, proinflammatory and those associated with Th1 determine the development and progression of the disease, while regulatory T cells exert an antiatherogenic activity (21). These cytokines are also involved in the pathogenesis of IBD by activating Th1 and Th 17 cells in CD and Th2 in UC (8).

The cytokine IL-6 can affect several mediated cell types, either by binding to the membrane of the IL-6 receptor or by binding to soluble IL-6 receptors. Therefore, IL-6 participates in the pathogenesis of multiple inflammatory disorders. IL-6 signaling inhibitors are commonly used to treat CD. The CANTOS multicenter randomized study published in 2018 showed that Canakinumab (a humanized monoclonal antibody targeting IL-1β) successfully reduces the rate of major cardiovascular events in the absence of any lipid-lowering effects (22).

JAK-STAT signaling pathways regulate the activity of several mediators, including IFN 1, IFNγ and IL- 2,4,6,7,9,12,15,21,23 and 27, involved in the pathogenesis of inflammatory bowel disease (23,24).

Tofacitinib is an oral inhibitor of JAK, especially for JAK1 and JAK3, demonstrating its efficacy in the treatment of UC. The OCTAVE study published in 2017 demonstrated the effectiveness of treatment in patients with moderate or severe active form of UC, used in induction and supportive therapy (25).

According to the two studies, both Canakinumab and Tofacitinib have an increased risk of severe and mild to moderate infections.

Atherosclerosis and intestinal microbiota

Impairment of the intestinal microbiota in patients with IBD may be associated with the development of atherosclerosis. The final conclusion of this study was that indole and its kyn / trp ratio derivatives, I3P and I3A, are associated with advanced atherosclerosis, while phenyl derivatives of hippuric acid may be correlated with the occurrence of severe cardiovascular events (26, 27).

Imbalance of the intestinal microbiota can increase the risk of cardiovascular disease in IBD by deteriorating intercellular connections, but also by increasing intestinal permeability. Endotoxins, especially lipopolysaccharides, from the intestine can enter the circulatory system and can intensify the process of atherogenesis by chronic systemic inflammation (26).

Types of diet in cvd and ibd

Consumption of simple carbohydrates can cause intestinal dysbiosis and inflammation, so a diet containing dietary fiber, carbohydrates and fats in a limited amount, can help reduce inflammation and remission in IBD (28).

The Mediterranean diet can reduce the cardiovascular risk by its action on the components of the metabolic syndrome, determining the improvement of the lipid and carbohydrate profile, the decrease of the body weight and of the waist circumference (29). Although this diet may be beneficial in patients with IBD, some rules are more difficult to follow, such as eating fresh vegetables and fruits. However, patients with IBD should follow this diet as much as possible depending on tolerance, having beneficial effects by reducing the risk of CVD (26).

Comparing the Mediterranean diet with Western dietary patterns, current studies show that they determine an excessive production of proinflammatory cytokines, associated with a reduction in the synthesis of anti-inflammatory cytokines. Therefore, approaching a healthy diet, based on an increased intake of fruits, vegetables, legumes, nuts and whole grains, helps reduce inflammation, thus preventing the risk of cardiovascular disease (30,31).

The multicenter EPIC cohort study showed that the western diet can cause the imbalance of the intestinal flora, being associated with an increased risk of CD and UC (32).

A recent meta-analysis in 2020 also confirms that a pro-inflammatory diet contains a high intake of refined cereals, red and processed meat, animal protein, animal fats and high-fat dairy products, as well as low fruit consumption. and fresh vegetables,

may increase the risk of developing inflammatory diseases (33).

Vitamin D and the risk of atherosclerosis in CVD and IBD

Vitamin D can reduce the risk of atherosclerosis by decreasing the accumulation of low-density lipoproteins (LDL) in macrophages, which will inhibit the formation of atherosclerotic plaque (34). It also reduces the risk by modulating the inflammatory response and decreasing the expression of pro-inflammatory cytokines: TNF- α, IL-6, IL-1 (35).

The chronic inflammatory condition in IBD causes a state of hypercoagulability by increasing the average volume of platelets leading to an increased risk of thromboembolic events. The presence of vitamin D will modulate thrombmodulin expression, blocking platelet aggregation and thrombogenic activity (26).

IBD treatment and CVD risk

Currently IBD treatment is based on 5 - ASA, corticosteroids, immunomodulatory therapy and biological therapy (TNF-α antagonists, vedolizumab, ustekinumab and tofacitinib) (36). In a Danish cohort study that included 23,833 patients, its demonstrated that those who received 5-ASA had a lower risk of ischemic heart disease compared to patients who never received it (37).

Another cohort study in 2020 showed that treatment with anti-TNFα agents causes a decrease in the risk of acute arterial events. Therapy with anti-TNFα agents targets several risk factors associated with cardiovascular disease: improved lipid profile, a endothelial function and arterial stiffness (1).

Conclusions

Clinicians should be aware of the increased risk of atherosclerotic cardiovascular disease. Therefore, early detection of patients with IBD and determination of cardiovascular risk factors is of utmost importance for early intervention and change the risk of cardiovascular disease.

Further studies are needed to identify risk factors in the early stages so as to assess risk stratification and optimal treatment.

It is recommended to perform screening for atheroscletic cardiovascular disease, especially in young patients (≤50 years), as well as in female patients, these representing the groups with the highest risk. Supplementary, should be emphasized the proper choice of medications, diet, vitamin D supplementation and promoting an active and healthy lifestyle.

Abbreviations:
5-ASA: 5-aminosalicylic acid
ASCVD: Atherosclerotic cardiovascular disease
CC1 :chemokine receptor antagonist 1
CCR5: chemokine receptor antagonist 5
CD: Chron's disease
CX3C :chemokine family
HR : Hazard ratio
I3A: Indole-3-aldehyde
I3P: Indole-3-propionic acid
IBD : Inflammatory bowel disease
ICAM-1: Intercellular Adhesion Molecule-1
IFN 1: Interferon type I

IFNγ : Interferon gamma
IL-1 : Interleukin- 1
IL-1β: Interleukin 1β
IL-6 : Interleukin- 6
JAK 1: Janus kinase 1
JAK 3: Janus kinase 3
Kyn: Kyneurine
LDL: Low density lipoprotein
MI: Myocardial infarction
NO : nitric oxid
RR: Risk ratio
Th1: T1 helper cell
Th17: T17 helper cell
Th2: T2 helper cell
TNFα: Tumor necrosis factor α
Trp: Tryptophan
UC: Ulcerative colitis
VCAM-1 :Vascular Cell Adhesion Molecule1

Conflict of Interest

Authors have no conflict of interest to disclose.

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