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REVIEW ARTICLE

ATHEROSCLEROTIC CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Summary

Inflammatory bowel disease (IBD) is associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD). This article reviews the epidemiology, pathophysiology, risk factors and treatment implications of ASCVD in IBD patients. A number of processes are involved in the increased risk of ASCVD, including inflammation, endothelial dysfunction, hypercoagulability, platelet abnormalities, dyslipidaemia, gut microbiome abnormalities and the use of corticosteroids. While the precise pathophysiology remains complex, the management of inflammation and cardiovascular risk factors is essential to reduce the risk of atherosclerosis in IBD patients. Collaboration between gastroenterologists and preventive cardiologists is emphasised for risk factor management and promotion of disease remission.

Key words: cardiovascular disease; inflammatory bowel disease; chronic inflammation; atherosclerosis

Introduction

Cardiovascular disease (CVD) is the most common cause of death in Europe, where coronary heart disease (CHD) contributes to 45 % of deaths among women and 39 % among men (1). Intensive research in recent years has shown that patients with chronic inflammatory diseases (rheumatoid arthritis, psoriasis, systemic lupus erythematosus) are at substantially higher cardiovascular risk because the chronic inflammation accelerates the processes of atherogenesis and thrombosis (2, 3). Inflammatory bowel disease (IBD) comprises Crohn's disease and ulcerative colitis, which are chronic inflammatory diseases of the digestive tract accompanied by chronic systemic inflammation and extraintestinal manifestations. Several meta-analyses have shown that IBD is associated with an increased risk of cardiovascular complications (4, 5). Cardiovascular complications in IBD patients include venous thromboembolism, atherosclerotic cardiovascular disease, heart failure, myocarditis, pericarditis, infective endocarditis and some types of cardiac arrhythmias (6, 7). This review article focuses mainly on complications related to atherosclerosis and atherothrombosis.

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Quick Takes

- Patients with IBD are at increased risk of cardiovascular complications.
- Several mechanisms have been proposed to explain increased cardiovascular risk in IBD: systemic inflammation, endothelial dysfunction, coagulation abnormalities, altered lipid metabolism, or drug effects (corticosteroids).
- The goal of IBD patient care is to achieve disease remission and to screen and reduce cardiovascular risk factors.
- Collaboration between gastroenterologists and cardiologists is crucial.

Epidemiology

Cardiovascular disease

In 2019, 12.7 million new cases of cardiovascular disease were recorded in the 57 member countries of the European Society of Cardiology. An estimated 113 million people in these countries were living with cardiovascular disease in 2019. The median age-standardised prevalence of cardiovascular disease across the member countries was 6,595 cases per 100,000 population. The median age-standardised incidence of cardiovascular disease across the member countries was 747.6 cases per 100,000 population (1).

In the Czech Republic in 2019, the age-standardised prevalence of CHD was 3,406 cases per 100,000 population and the incidence was 364 cases per 100,000 population (1).

Inflammatory bowel disease

Globally, the age-standardised prevalence of IBD in 2017 was 84.3 cases per 100,000 population; in the Czech Republic the prevalence was 160-180 cases per 100,000 population and in the USA the prevalence was 464 cases per 100,000 population. Incidence is highest between the second and fourth decade of life (8).

The relationship between cardiovascular disease and idiopathic inflammatory bowel disease

Patients with IBD have a higher risk of cardiovascular complications. The independent relationship between IBD and CHD has been shown in several meta-analyses (4, 5, 9). These include in particular a meta-analysis from 2017, which comprised ten cohort studies and showed that there is an increased risk of CHD with IBD (RR 1.24; 95 %, CI 1.14-1.36). This increased risk was more pronounced among women and younger patients (4). The authors of a 2018 meta-analysis reached similar conclusions, showing that there is an association between IBD and CHD (RR 1.17, CI 1.07-1.27) as well as an association between IBD and myocardial infarction (RR 1.12, CI 1.05-1.21) (5).

Table 1. IBD and ASCVD. The key studies cited above.

Study	Year	Study type	Study members	Results
Sun H.H. et al.	2018	Meta-analysis	27 studies	Pooled RR of 1.25, 1.17 and 1.12 for cerebrovascular disease, coronary heart disease and myocardial infarction in IBD patients vs controls.
Feng W. et al.	2017	Meta-analysis	10 cohort studies	Increased risk of ischemic heart disease, especially in Crohn's disease (RR 1.24).
Rungoe C. et al.	2013	Cohort study	28,833 pts	Increased risk of IHD within the first year after IBD diagnosis (IRR = 2.13) and 1.22 during the next follow up.

Pathophysiology

IBD refers to chronic inflammatory disease affecting the digestive tract. Patients with IBD are, like patients with other chronic inflammatory diseases (rheumatoid arthritis, psoriasis, systemic lupus erythematosus), at higher risk of atherosclerotic cardiovascular disease (ASCVD) (3, 5, 10). The precise pathophysiological relationship between IBD and ASCVD is not known. Researchers' attention is focused on a range of processes that are activated in patients with IBD and directly or indirectly potentiate the development of atherosclerosis. These include local and systemic inflammation, endothelial dysfunction (11), hypercoagulability and thrombocyte abnormalities (12), lipid metabolism disorders (13), gut microbiome abnormalities (14) and the use of corticosteroids (15).

Chronic inflammation affects every stage in the development of atherosclerosis (16). Various cells of the immune system (T and B lymphocytes, macrophages), proinflammatory and anti-inflammatory cytokines and chemokines are involved in immunological processes in patients with IBD and also in the development of atherosclerotic plaque. Chronic inflammation modifies the physical and functional features of the vascular wall and disrupts the balance between vasodilatory and vasoconstrictive effects (17), which leads to endothelial dysfunction. Muscle tone increases in the smooth muscle tissue of the vascular wall, leukocyte adhesion and diapedesis increase, the regulation of cell adhesion molecules (VCAM-1, ICAM-1) is disrupted, and procoagulant activity increases (18, 19). Endothelial dysfunction is the initial process in the pathogenesis of atherosclerosis and is considered an independent predictor of the development of ASCVD. In patients with IBD, endothelial dysfunction is related both to the severity of inflammation and to the duration of the inflammation (20). Patients with IBD were found to have dysregulation of E-selectin, vascular endothelial growth factor (VEGF), ICAM-1, MADCAM-1, circulating and local adhesion molecules (21, 22). Similarly, these patients have increased production of the vasoconstrictor endothelin (23) and reduced production of vasodilating nitric oxide (24). The concentration of circulating endothelial progenitor cells (CEPs), which enable the direct repair of damaged endothelium in the vascular wall, is reduced (25), while there is an increased concentration of lipopolysaccharide (LPS), which can upregulate the expression of pro-inflammatory cytokines (26).

Systemic inflammation in IBD patients induces a hypercoagulable state (abnormalities in coagulation, fibrinolysis and platelet function) (12, 27, 28). This significantly increases the risk of thromboembolic events (TE). Subclinical activation of the coagulation system includes increased thrombin generation, tissue factor activation, protein C pathway dysfunction and impaired fibrinolytic activity (12). Platelet production and reactivity are also increased. There is a tendency for platelet-platelet and platelet-leukocyte aggregates to form (12, 29–31). Patients with IBD have a two to three times higher risk of developing venous thromboembolic events (VTE) (32, 33). This risk is particularly pronounced during acute flares (32), following recent hospitalisation for flares (34), during corticosteroid use (34, 35), in IBD complicated by abscess, stenosis or fistula (34), and associated with surgical treatment of the disease (36). Deep vein thrombosis of the lower limbs and pulmonary embolism are the most common types of VTE (37). Less commonly, VTE affects the portal vein, mesenteric vein or splenic vein (38). Arterial thromboembolism (ATE) is less common in IBD than VTE (39). ATE comprises thrombosis of the coronary arteries (4, 5, 9), cerebral arteries (40), carotid arteries (41), splanchnic arteries (42), lower and upper extremity arteries (43) and aorta (44). Intensive research is underway into the exact pathophysiology of thromboembolism in IBD patients.

Patients with IBD have lower levels of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-c) compared to healthy individuals. Regarding the levels of triglycerides and high density lipoprotein cholesterol (HDL-c), there are no significant differences between IBD patients and healthy individuals (13, 45). These findings remain valid regardless of the disease activity (13) and even after excluding individuals using hypolipidemic drugs from the study group (45). Chronic inflammation, in general, is associated with atherogenic small dense LDL-c and dysfunctional HDL-c (20, 46). Chronic inflammation, together with malnutrition, malabsorption, and altered intestinal transit, are potential mechanisms leading to lipid metabolism abnormalities in IBD (47).

Risk factors

The "traditional" risk factors for atherosclerosis include arterial hypertension, hypercholesterolemia, obesity, smoking, insulin resistance and diabetes mellitus (48). Certain high-risk habits are known to be associated with both IBD and CHD. These include a "Western" lifestyle (49), anxiety, psychological stress (40, 50), and for Crohn's disease also smoking (51).

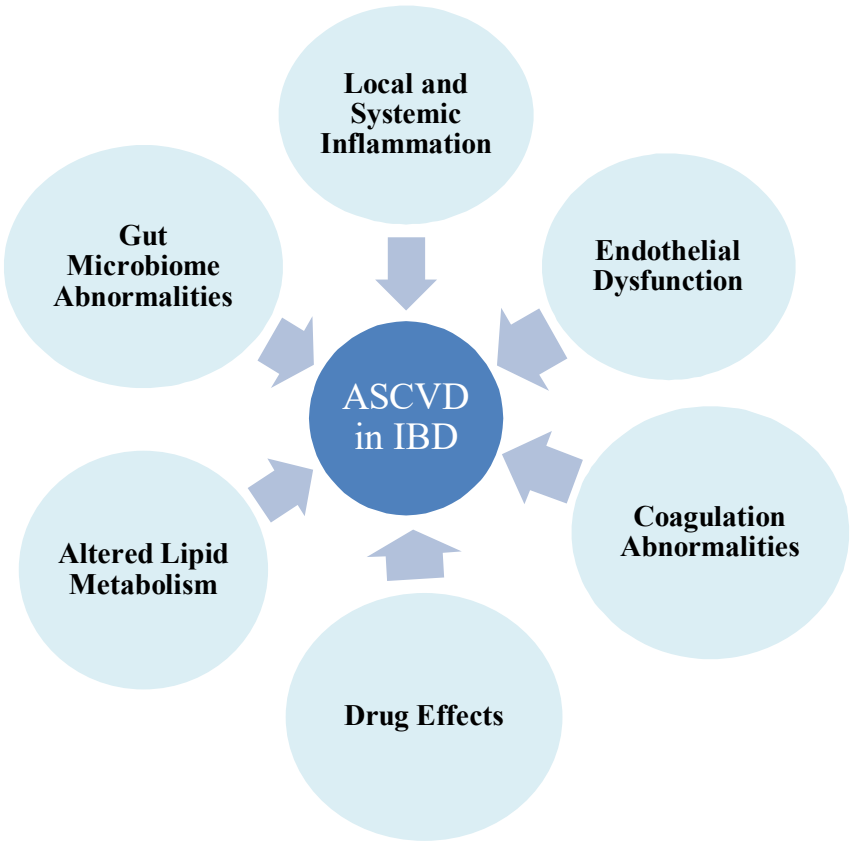

Figure 1. Potential pathophysiological mechanisms of ASCVD development in IBD.

In addition to these factors, chronic inflammation, which leads to endothelial dysfunction by an incompletely understood pathway involving pro-inflammatory cytokines (e.g. TNF-α, IL-1, IL-6), also plays a role in the development of atherosclerosis (11). Independent of traditional cardiovascular risk factors, elevated plasma CRP concentrations are associated with an increased risk of acute myocardial infarction and stroke (52). Some of the most important pro-inflammatory and pro-thrombotic cytokines that are linked to IBD include TNF-α, IL-6, and IL-1 (53). Several authors have suggested that IL-1 and IL-6 are involved in cardiovascular and cerebrovascular disease (54, 55). IL-1 induces the expression of cellular adhesion molecules, thus facilitating the adhesion of leukocytes to the vascular endothelium (56). IL-6 is the most relevant procoagulant cytokine. It has the potential to increase blood levels of fibrinogen, plasminogen activator inhibitor type 1, 5, 7, and CRP (57). TNF-α has been demonstrated to enhance thrombosis by inducing platelet activation and platelet-mediated thrombus formation, increasing tissue factor (through the NF-κB pathway), and decreasing protein C activation by endothelial cells (58–60). This activation of coagulation factors can further upregulate TNF-α (58).

Another link between IBD and CVD may be dysbiosis. Changes in the gut microbiota can affect organs, tissues, and processes beyond the digestive tract. Thus, they may also interfere with atherosclerosis (61, 62). Increased levels of bacteria from the Enterobacteriaceae family have been found in both IBD and CVD (63). Reduced levels of butyrate-producing bacteria have also been found in both IBD and CVD. Since butyrate is thought to have an atheroprotective effect, this may be an interesting finding (64–66).

The effects of IBD treatment on atherosclerosis development

5-aminosalicylates, corticosteroids, immunosuppressants and biological therapy are used in IBD pharmacotherapy; more broadly, treatment may also involve probiotics, antibiotics, enteral and parenteral nutrition.

Table 2. IBD treatment and its effect on the development of ASCVD.

IBD Treatment	Effect on ASCVD
5-ASA	may reduce the risk of ASCVD
Corticosteroids	increase the risk of ASCVD
Immunomodulators	not known
Biologics	research is ongoing
JAK inhibitors	research is ongoing

5-ASA: Aminosalicylates, similar to aspirin, have anti-inflammatory, anti-oxidant and antiplatelet effects (67). IBD patients taking 5-ASA have a significantly lower risk of coronary heart disease compared to patients not taking 5-ASA (9).

Glucocorticoids: Long-term glucocorticoid therapy increases the risk of arterial hypertension, dyslipidaemia, obesity and insulin resistance. Patients with IBD who have been treated with corticosteroids are at higher risk of ASCVD; this risk depends on the dose of corticosteroids (68).

Immunomodulators (methotrexate and thiopurines): The effect of treatment with methotrexate or thiopurines on the development of ASCVD is unknown (6). Thiopurines are thought to have a protective effect by reducing TGF-β and IL-10 production (69). According to Woodman *et al*, methotrexate may have a beneficial effect on arterial stiffness in patients with rheumatoid arthritis (70).

Biologics: There is no evidence of an increased risk of ASCVD with either vedolizumab or ustekinumab (71, 72). The biological effects of anti-TNF-α agents are complex. TNF-α is proatherogenic (6). The effect of anti-TNF-α agents on lipid profile is not yet fully understood. According to the study by Koutroubakis *et al*., the levels of TC, HDL cholesterol and apo-A1 are significantly increased after treatment with infliximab as compared to the baseline values (73). The study by Miranda-Bautista *et al*. showed that long-term treatment of normolipidemic IBD patients resulted in sustained significant increases in TC and LDL-c (74). On the other hand, other studies have yielded conflicting results. Some have shown no difference in the lipid profile of IBD patients treated with anti-TNF-α. Inhibiting TNF-α causes abdominal fat to increase. In contrast, TNF-α inhibition has a beneficial effect on insulin resistance, endothelial function, arterial stiffness and fibrinolysis (75, 76).

JAK inhibitors: Janus kinase (JAK) inhibitors are synthetic, orally administered, small molecules that inhibit intracellular signaling of a variety of mediators. JAK inhibitors cause dyslipidemia, which may lead to increased cardiovascular risk (6). In patients with ulcerative colitis, tofacitinib has been associated with reversible changes in TC, HDL-c, and LDL-c (77, 78). A meta-analysis conducted in 2020 evaluated the safety profile of tofacitinib, upadacitinib, filgotinib, and baricitinib in patients with rheumatoid arthritis, inflammatory bowel disease, psoriasis, and ankylosing spondylitis. Thirty studies evaluated MACE in 32,665 patients treated with JAK inhibitors. The MACE incidence rate was 0.67 per 100 patient-years (79).

Overall, it may be inferred that therapeutic efforts to reduce the intensity of inflammation may reduce the risk of developing ASCVD.

Current guidelines

The ESC 2021 guidelines (80) also briefly address chronic inflammatory diseases. The authors consider that patients with rheumatoid arthritis have an increased risk of cardiovascular disease of about 50% (81), while patients with IBD have an increased risk of about 20% (82). For each patient with a chronic inflammatory disease, it is appropriate to consider their individual cardiovascular risk and to take the presence of chronic inflammation into account when deciding on preventive measures. Optimal anti-inflammatory therapy is essential for patients

with chronic inflammatory diseases. Regarding cardiovascular risk, these patients should be treated in the same way as the general high-risk population (80).

Future directions

- Detailed understanding of the molecular pathophysiological mechanisms leading to accelerated atherosclerosis in IBD patients, especially the immunological mechanisms involved in atherothrombosis pathogenesis, inflammation pathogenesis and IBD development.
- Individual cardiovascular risk assessment, identification of patients at highest cardiovascular risk and effective targeted therapy.
- In the context of coronary artery disease risk stratification in IBD patients, the Fat Attenuation Index Score (FAI-Score) appears to be a promising method for the future.
- Establishment of a clear target for preventive measures that will result in both a reduction in inflammation and a reduction in cardiovascular risk.
- Cost-effectiveness must also be considered in the type, extent and frequency of these preventive measures.

Discussion

Two meta-analyses have revealed an increased incidence of cardiovascular disease in patients with IBD (4, 5). This positive association is particularly evident in women (5). On the other hand, neither the 2013 meta-analysis by Bewtra *et al*. (83) nor the 2018 meta-analysis by Sun and Tian (5) found increased cardiovascular mortality in patients with Crohn's disease or ulcerative colitis. A possible explanation for this phenomenon is that patients with IBD are younger on average, in good biological condition and have sufficient physical reserves to cope with acute stroke or acute myocardial infarction resulting in non-fatal cardiovascular events.

Treatment for patients with IBD should, among other things, aim to reduce their cardiovascular risk; close collaboration between gastroenterologists and preventive cardiologists is therefore necessary. The risks of atherosclerotic cardiovascular complications and of ischemic stroke are most pronounced in patients with prolonged active disease, during disease exacerbation and in patients using corticosteroids. From this perspective, it is fundamentally important to achieve disease remission. We should actively investigate all cardiovascular risk factors (smoking, lifestyle, blood pressure, glucose, lipids) and aim to minimise them.

Conclusion

In both IBD and CHD, chronic inflammation is a common denominator. Managing inflammation, as well as other cardiovascular risk factors, is therefore crucial to reducing the risk of accelerated atherosclerosis and associated complications. This can be achieved through a proactive, multidisciplinary, team-based approach.

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Conflict of interest

Authors declare no conflict of interests.

Adherence to Ethical Standards

This article does not contain any studies involving animals performed by any of the authors.

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