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Cardiovascular disease: extraintestinal manifestation of inflammatory bowel disease

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Inflammatory bowel disease (IBD) is a spectrum of diseases characterized by the interplay of the aberrant immune system, genetic factors, environmental factors, and intestinal microbiota, resulting in relapsing inflammation of the gastrointestinal tract. Underlying pro-inflammatory state and immune dysregulation act as a catalyst for increasing the likelihood of developing extraintestinal manifestations, including cardiovascular diseases (CVD) like atherosclerosis, pericarditis, myocarditis, venous and arterial thromboembolism, arrhythmias, despite a lower prevalence of classic CVD risk factors, like high body mass index or dyslipidemia compared to the general population. Chronic inflammation damages endothelium resulting in the recruitment of inflammatory cells, which induce cytotoxicity, lipoprotein oxidation, and matrix degradation, which increases the risk of atherosclerosis. Additionally, intestinal dysbiosis disrupts the intestinal mucosal barrier, releasing endotoxins and lipopolysaccharides into circulation, further exaggerating the atherosclerotic process. Abnormal collagen metabolism and alteration of nitric oxide-mediated vasodilation lead to blood pressure dysregulation in patients with IBD. Therefore, it is essential to make lifestyle modifications like smoking cessation, dietary changes, and increasing physical activity with adherence to medication to mitigate the risk of developing CVD in patients with IBD. This article reviews the potential links between IBD and the increased risk of CVD in such individuals. **(Intest Res, Published online)**

Key Words: Inflammatory bowel disease; Intestinal dysbiosis; Cardiovascular diseases; Immune dysregulation

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic systemic inflammatory disorder that affects over 6.8 million people worldwide and has been found to impact more than 1 million Americans and 2.5 million Europeans, with more prevalence among women in Western populations and men in Eastern populations.[1] Studies have shown that African American, Hispanic, and Asian patients are more susceptible to IBD than Caucasians.[2] Additionally, people with lower levels of education, unemployment, poverty, or living in suburban areas are at a higher risk for IBD.[3] Certain medical treatments and procedures, such as immunomodulators, colectomies, and fecal microbiota transplantation, may also potentially lead to the development or worsening of IBD,[4] classified as ulcerative colitis (UC) and Crohn's disease (CD), mainly presents with recurring abdominal pain, diarrhea, nausea, and vomiting over time. The CD is distinguished by its transmural inflammation and segmental intestinal involvement, typically affecting the terminal ileum, with epithelioid granulomas on histology. In contrast, UC exhibits a widespread pattern of mucosal inflammation and primarily impacts the rectum, with varying progression toward the terminal ileum.[5] UC and CD result from a combination of factors, including an aberrant immune system, genetic factors, environmental factors, and intestinal microbiota[6] leading to

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increased synthesis of cytokines.[7] Thus, underlying pro-inflammatory state and immune dysregulation catalyze various cardiovascular manifestations in patients with IBD despite a lower prevalence of classic cardiovascular diseases (CVD) risk factors, like high body mass index (BMI) or dyslipidemia, compared to the general population.[8] CVD are the most prevalent cause of death worldwide. As per the World Health Organization (WHO), an estimated 17.3 million people died from CVDs in 2008, primarily heart disease and stroke.[9] Patients with IBD are more likely to develop early atherosclerosis and myocardial infarction, and CVD risk is higher when a disease is active.[10] It has been demonstrated that the risk of acute myocardial infarction, stroke, and cardiovascular death was significantly higher during IBD exacerbations but similar to the control group during remission, suggesting that the release of inflammatory mediators and cytokines during the active phase linked to an increased risk of CVD. According to another study, IBD patients had a roughly 3-fold higher risk of venous thromboembolism than people without the condition, and disease flares further increased this risk.[11] Additionally, it is thought that individuals with severe IBD experience malabsorption of several minerals and antioxidants, such as vitamin C, which worsens oxidative stress.[12] IBD is a debilitating condition in itself, and given the rising prevalence of IBD and its reported CVD consequences, which can lead to a higher mortality rate, it is critical to determine the triggers causing an elevated CVD risk in this patient population. This article seeks to explore the impact of probable inflammatory, dietary, and genetic factors in IBD patients that may raise the risk of CVD, as well as how IBD and its therapies modify atherosclerotic CVD (ASCVD) risk factors in IBD patients and offer a clinical approach to preventing ASCVD in this population.

Table 1. Various Studies Discussing the Relationship between IBD and CVD

Study	Year	Methods	Conclusions
Andersohn et al.[13]	2010	Case-control study included 8,054 IBD patients and 161,078 controls	Stratified analyses showed that the risk was higher in younger patients under 50 (OR, 2.93; 95% CI, 1.44–5.98) than in older patients (OR, 0.99; 95% CI, 0.75–1.30, *P* for interaction = 0.01).
Yarur et al.[14]	2011	Prospective cohort study included 356 IBD patients and 712 controls	The HR for developing CAD between groups was 4.08 (95% CI, 2.49–6.70) after adjusting for (hypertension, diabetes, dyslipidemia, and obesity).
Haapamäki et al.[15]	2011	Cross-sectional study included 2,831 IBD patients	IBD patients experienced coronary heart disease substantially more frequently than their peers (*P* = 0.004). The difference was more pronounced in females (*P* = 0.014 as opposed to *P* = 0.046 in males).
Sridhar et al.[16]	2011	Cross-sectional study	IBD is positively linked with dysrhythmias in females aged 18 to 39 years, according to a stratified analysis of age and gender (aOR, 2.05; 95% CI, 1.72–2.44).
Rungoe et al.[17]	2013	Retrospective cohort study	Within the first year following the diagnosis of IBD, there was a significantly elevated risk of IHD (IRR, 2.13; 95% CI, 1.91–2.38). Following an IBD diagnosis, the risk of IHD was 1.22 (95% CI, 1.14–1.30) over the subsequent 1–13 years of follow-up.
Kristensen et al.[18]	2013	Retrospective cohort study with 20,795 cases of IBD and 199,978 controls	IBD patients exhibited a higher risk of MI, stroke, and cardiovascular mortality. The risk ratios for MI rose to 1.49 (95% CI, 1.16–1.93) and 2.05 (95% CI, 1.58–2.65) during flares and chronic IBD activity, as well as to 1.53 (95% CI, 1.22–1.92) and 2.50 (95% CI, 2.14–2.92) for cardiovascular mortality.
Kristensen et al.[19]	2014	Prospective cohort study with 23,681 cases of IBD and 5,412,966 non-IBD	Patients with IBD had a 37% higher chance of being hospitalized for heart failure (IRR, 1.37; 95% CI, 1.26–1.49) and a higher risk of heart failure hospitalization during flares (IRR, 2.54; 95% CI, 2.13–3.04).
Panhwar et al.[20]	2019	A case-control study with 290,430 IBD patients and 28,799,790 non-IBD patients	UC and CD had a greater rate of MI (UC 6.7%, CD 8.8%, and non-IBD 3.3%; OR for UC 2.09 [95% CI, 2.04–2.13] and CD 2.79 [95% CI, 2.74–2.85]). Age had a significant impact on the risks of MI, with the odds being greatest in younger patients (age 30–34 years: OR 12.05 [95% CI, 11.16–13.01], age > 65 years: OR 2.08 [95% CI, 2.04–2.11]) and decreasing with age (aOR, 1.25; 95% CI, 1.24–1.27).
Biondi et al.[21]	2020	Case-control study with 52 IBD and 37 healthy controls	Atherosclerotic carotid plaque (25% vs. 5.4%, *P* = 0.032) and carotid intima-media thickness (0.690.12 mm vs. 0.630.12 mm, *P* = 0.031) were greater in the IBD group than in the control group.

IBD, inflammatory bowel disease; CVD, cardiovascular disease; OR, odds ratio; CI, confidence interval; HR, hazard ratio; aOR, adjusted OR; IRR, incidence rate ratio; IHD, ischemic heart disease; MI, myocardial infarction; UC, ulcerative colitis; CD, Crohn's disease.

EPIDEMIOLOGY OF CVD IN IBD PATIENTS

Several studies have shown a relationship between IBD and risk factors such as younger age (less than 50 years), female sex, and increased risk of CVD during acute flare (Table 1).[13-21]

A case-control study by Andersohn et al.[13] and Panhwar et al.[20] found that younger IBD patients (under 50 years old) have a higher risk of CVD (Table 1). Cross-sectional studies by Haapamäki et al.[15] and Sridhar et al.[16] determined that female IBD patients are more likely to experience coronary heart disease. A retrospective cohort study conducted by Rungoe et al.[17] and Kristensen et al.[18] observed an increased risk of CVD during the acute flares of IBD.[17,18]

Kristensen et al.[19] performed a prospective cohort study with 23,681 cases of IBD and 5,412,966 non-IBD, which concluded hospitalization for heart failure occurred in 553 participants with IBD and 171,405 in the reference population with a mean follow-up of 11.8 years in the reference population and 6.4 years in the group with IBD. Compared to the reference population, patients with IBD had a 37% higher chance of being hospitalized for heart failure (incidence rate ratio [IRR], 1.37; 95% confidence interval [CI], 1.26–1.49). IBD activity-specific analyses revealed a significantly higher risk of heart failure hospitalization during flares (IRR, 2.54; 95% CI, 2.13–3.04) and persistent activity (IRR, 2.73; 95% CI, 2.25–3.33) but not in IBD remission (IRR, 1.04; 95% CI, 0.94–1.16).[19] A case-control study with 52 IBD and 37 healthy revealed atherosclerotic carotid plaque (25% vs. 5.4%, $P=0.032$) and carotid intima-media thickness (0.690.12 mm vs. 0.630.12 mm, $P=0.031$) were greater in the IBD group than in the control group. According to a multivariate logistic regression analysis, IBD patients had a 6.45-fold greater chance of developing carotid atherosclerotic plaque (odds ratio, 6.45; 95% CI, 1.035–40.216; $P=0.046$).[21]

EPIDEMIOLOGY OF RISK FACTORS OF CVD IN IBD PATIENTS

IBD and CVD share an array of risk factors like smoking, dyslipidemia, and obesity, increasing the severity of each other. Risk factor, like smoking, is identified as one of the most important modifiable risk factors for CVD as various toxins in tobacco smoke injure the endothelium and initiate the cascade of inflammation and thrombosis.[22] Similarly, smoking alters intestinal microbiota and increases inflammation in the ileum by increasing intestinal barrier permeability and altering Paneth cell function, leading to increased susceptibility to bacterial infection. Cigarette smoke can also promote intestinal inflammation via an interleukin (IL)-17 response, which enhances intestinal Th17 cells and neutrophils.[23] Smoking significantly increases the risk of developing and worsening CD, yet protects against the development and reduces the severity of UC.[24] A meta-analysis conducted by Calkins[25] showed smoking association with CD, as the study discovered that smokers have a higher risk of CD with a pooled odds ratio of 2.0 compared to nonsmokers. In addition, smoking also increases the risk of recurrence or relapse of CD. Cottone et al.[26] observed smoking as an independent risk factor for clinical, surgical, and endoscopic recurrence in a group of 182 patients who had undergone surgery for CD over almost 20 years. The study also found that smoking worsens the severity of clinical and endoscopic recurrence. The impact of smoking on UC is wholly reversed to CD.[27] In a meta-analysis of 9 case-control studies, the risk of developing UC was lower in current smokers than in nonsmokers. The analysis showed that the lifetime risk of nonsmokers acquiring UC was 2.9 times higher than that of smokers. The risk was also found to be higher for former smokers as compared to nonsmokers. A dose-response relationship was observed in the study, indicating a lower risk of disease with increasing levels of smoking. However, some subsequent studies supported this data or failed to recognize the dose-response relationship.[25]

Dyslipidemia is also a significant risk factor for the development and progression of CVD.[28] However, several studies have indicated that individuals with IBD have a lower burden of traditional risk factors for atherosclerosis, including obesity, diabetes mellitus, and dyslipidemia. Thus strengthening the link between nontraditional risk factors, such as chronic inflammation, and the development of atherosclerosis in IBD patients.[29] A study by Wang et al.[30] examined the lipid profile and disease activity in patients with IBD and found that patients with CD and UC had lower levels of total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol than the control group. In a study conducted by Sappati Biyyani et al.[31] in India, traditional atherosclerotic risk factors were evaluated in patients with IBD and coronary artery disease (CAD) compared to a control group (only CAD). The study used the Framingham risk score, a 10-year risk of CAD score based on risk factors such as age, hypertension, diabetes mellitus, tobacco use, and dyslipidemia. The study found that among 42 cases and 137 controls, the Framingham risk score was significantly lower in patients with

IBD and CAD than in controls (8.1 vs. 10.0, $P=0.002$).[31] In a cohort study by Moon et al.[32] investigating trends and environmental risk factors of CD in South Korea, A total of 14,060,821 people aged over 40 years who underwent national health screening in 2009 were followed up until December 2017. During the follow-up period, 1,337 out of 100,000 patients developed CD. Men aged 40 to 64 years had a higher risk of developing CD than women, with an adjusted hazard ratio (aHR) of 1.46 and a 95% CI of 1.29–1.66. However, this difference tended to disappear as the age of onset increased. Among the middle-aged group, patients with a history of smoking (aHR, 1.46; 95% CI, 1.19–1.79) and anemia (aHR, 1.85; 95% CL, 1.55–2.20) had a significantly higher CD risk. Even in the elderly group (aged 65 years and above), ex-smoking and anemia were found to increase the CD risk (aHR, 1.68; 95% CI, 1.22–2.30 and aHR, 1.84; 95% CI, 1.47–2.30, respectively). Particularly in the middle-aged group, those with CKD had a statistically elevated CD risk (aHR, 1.37; 95% CI, 1.05–1.79). Alcohol consumption and higher BMI are negatively associated with CD incidence in both age groups. In the middle-aged group, alcohol consumption (aHR, 0.77; 95% CI, 0.66–0.89) and higher BMI (aHR, 0.73; 95% CI, 0.63–0.84) were negatively associated with CD incidence. In the elderly group, alcohol consumption was negatively associated with CD incidence (aHR, 0.57; 95% CI, 0.42–0.78), while the association between higher BMI and CD incidence was not statistically significant (aHR, 0.84; 95% CI, 0.67–1.04). Regular physical activity and dyslipidemia negatively correlated with CD incidence in the middle-aged group, with an aHR of 0.88 (95% CI, 0.77–0.89) and 0.81 (95% CI, 0.68–0.96), respectively.[32]

Patients suffering from IBD are generally managed using topical steroids or more aggressive treatment like systemic steroids immunosuppression with another novel agent depending on the severity of the disease, as patients with mild disease (fewer than 4 loose stools per day, mild abdominal pain, typical lab test results for hemoglobin, erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP]) can be managed by topical steroids, and moderate to severe disease (more than 6 loose stools per day, severe abdominal pain, anemia, elevated ESR and CRP levels, tachycardia) require more aggressive treatment like systemic steroids, immunosuppression with another novel agent. While these treatments can effectively relieve IBD symptoms, concerns about their possible connection to ASCVD exist. For instance, corticosteroids have been associated with a higher risk of heart failure, thromboembolism, and insulin resistance. In contrast, anti-tumor necrosis factor (TNF) therapy lowers the baseline pro-coagulant imbalance of IBD patients with decreasing levels of fibrinogen and CRP and lowers the risk of thrombosis.[33] Lewis et al.[34] conducted a retrospective study on 7,694 CD patients taking prolonged corticosteroids and 1,879 taking anti-TNF therapy. It concluded that anti-TNF therapy might lessen aortic stiffness and is linked to a lower incidence of cardiovascular events for CD patients compared to long-term corticosteroid therapy.[34] By better understanding the role of gut microbiota in developing CVD, there is potential for developing new therapies that involve personalized dietary changes, prebiotic and probiotic supplements, postbiotics, trimethylamine N-oxide (TMAO) inhibitors, and fecal microbiota transplants. Fecal microbiota transplant has shown promising results in remission for those with mild to moderate UC and improving their endoscopic results. However, more research is required to assess the effectiveness and safety of fecal microbiota transplants for CVD.[35] To provide the best possible treatment, healthcare providers need to understand and assess the risk of CVD in patients with IBD. This involves using appropriate diagnostic tools, medications, and lifestyle changes tailored to each patient's needs.

PATHOPHYSIOLOGY

IBD is characterized by the recruitment and activation of a large number of immune and inflammatory cells within the gastrointestinal tract due to an abnormal immune response to gut microflora presenting as relapsing and remitting course of abdominal pain, diarrhea, nausea, and vomiting. Chronic systemic inflammation and immune dysregulation in IBD patients increase the susceptibility to various CVDs, as inflammatory cells like macrophages, monocytes, dendritic cells, and T cells play a central role in the pathogenesis of IBD and many CVDs (Table 2).[10,11,36] When activated, these cells release vasoactive molecules and pro-inflammatory cytokines, like TNF, interferon-gamma, IL-1, IL-6, IL-8, IL-12, promoting lipoprotein oxidation, cytotoxicity, and matrix component degradation. This leads to plaque destabilization, increased risk of rupture, and subsequent thrombosis.[37,38] Increased levels of these proinflammatory cytokines, along with elevated levels of CRP and homocysteine, result in accompanying changes in glucose and lipid metabolism, leading to increased LDL, triglycerides, insulin resistance, and decreased HDL. These alterations in the body increase the likelihood of developing ASCVD, obesity, and diabetes (Fig. 1).[39]

Intestinal dysbiosis is another mechanism that increases the risk of CVD in patients with IBD.[40] The impaired composi-

Table 2. Genetic Linkage between CVD and IBD[31]

Genes associated with IBD and CVD	Chromosome	Physiological functions	Association
NOD2	Chromosome 16	Involved in the innate immune process; activated by its ligand, leading to translocation of the (NF-kB)—a key transcription factor of pro-inflammatory cytokines into the nucleus	Atherosclerosis and IBD
CDK2NA, CDK2NB	Chromosome 9p21	Associated with cell proliferation, aging, and apoptosis	Atherosclerosis and IBD
Genetic polymorphism of *Stromelysin-1*	Chromosome 11q22.3	Member of MMP-3 regulating the accumulation of ECM during tissue injury	Atherosclerosis and IBD
Genetic polymorphism of *Apo E*	Chromosome 19q13. 32	Involved in Lipid Transport and have an immunomodulatory role by downregulate chemokine mRNA expression on intestinal epithelial cells	Atherosclerosis and IBD

CVD, cardiovascular disease; IBD, inflammatory Bowel Disease; NF-kB, nuclear factor kappa light chain enhancer of activated B cells; MMP-3, matrix metalloproteinase-3; ECM, extracellular matrix; mRNA, messenger RNA.

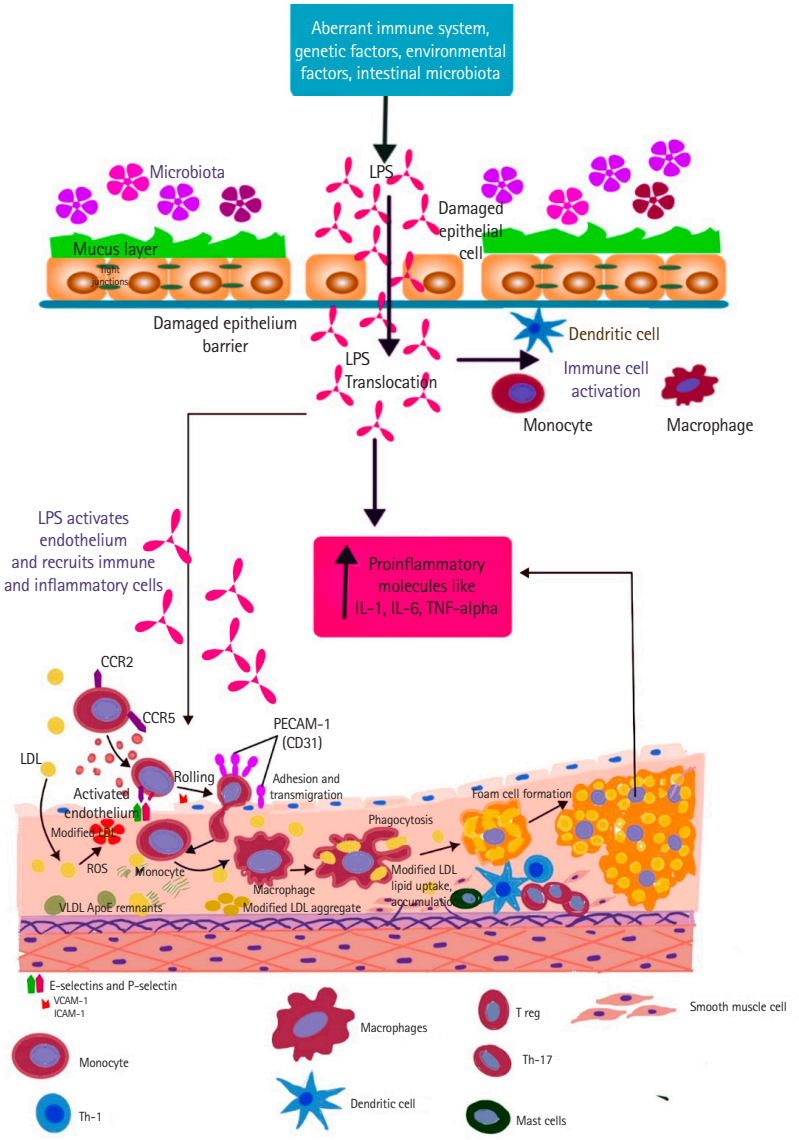

Fig. 1. Inflammatory bowel disease gut microbiome abnormalities may link to atherosclerotic cardiovascular disease. LPS, lipoprotein lipase; IL, interleukin; TNF, tumor necrosis factor; LDL, low-density lipoprotein; CCR, chemokine receptor; ROS, reactive oxygen species; VCAM-1, vascular cell adhesion molecule 1; ICAM-1, intercellular adhesion molecule 1.

tion of the intestinal microbiome in patients with IBD is associated with the development of atherosclerosis, as metabolites secreted by gut bacteria, such as indole and phenyl derivatives, exacerbate the advanced atherosclerotic process of the arteries and correlate with the occurrence of serious adverse cardiovascular events.[41] In addition, indole has a deleterious effect on blood pressure through peripheral and central mechanisms dependent on serotonin signaling.[10] Intestinal dysbiosis also damages the tight intercellular connections facilitating the translocation of microbial lipopolysaccharides (LPS) and other endotoxins into circulation. This LPS and other endotoxins activate various Toll-like receptors (TLRs). Upon activation, TLRs become dimerized and trigger the subsequent activation of downstream signaling cascades, such as inducing a variety of inflammatory cytokines through transcription by mediating the phosphorylation of inhibitor of nuclear factor kappa B (IκB) to activate nuclear factor kappa light chain enhancer of activated B cells (NF-kB) leading to vascular endothelins, which intensifies the process of atherogenesis.[42] In addition, the gut microbiota metabolism choline, phosphatidylcholine, and l-carnitine to produce trimethylamine (TMA), which is further oxidized in the liver into the proatherogenic metabolite TMAO, which plays a vital role in the pathogenesis of coronary heart disease (Fig. 2).[43] Furthermore, the microbiota in the gut plays a crucial role in the synthesis of bile acids. Normal gut microbial enzymes, like bile salt hydrolase, are necessary for deconjugation and dehydroxylation reactions involved in bile acid synthesis. An alteration in microbiota can decrease the production of these enzymes, resulting in a lower synthesis of bile acids, causing an increased risk for accumulation of cholesterol and triglycerides and predisposing to dyslipidemia and subsequent atherosclerosis.[44,45]

Patients with IBD exhibit elevated vascular smooth muscle tone due to decreased nitric oxide (NO) synthesis (Fig. 3). Pa-

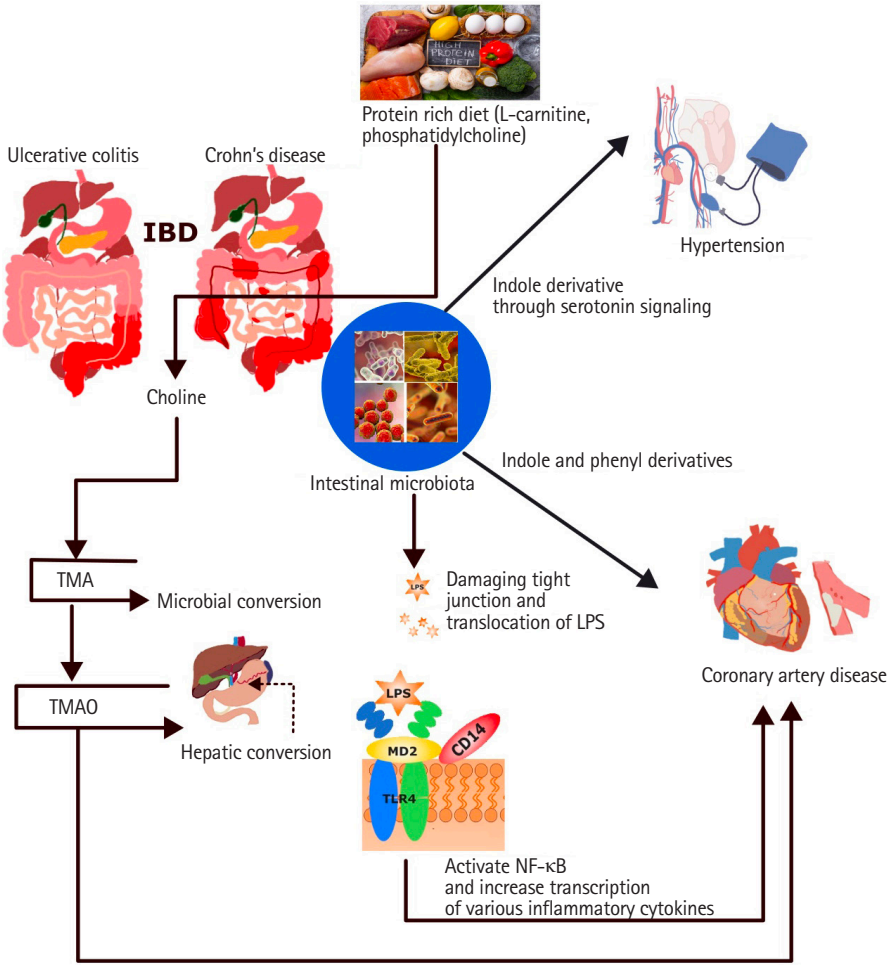

Fig. 2. Intestinal dysbiosis and cardiovascular disease. IBD, inflammatory bowel disease; TMA, trimethylamine; TMAO, trimethylamine-N-oxide; LPS, lipoprotein lipase; TLR, Toll-like receptor; NF-kB; nuclear factor kappa light chain enhancer of activated B cells.

tients suffering from IBD have an elevated amount of enzyme arginase, which competes for l-arginine, the substrate of NO. In addition, TNF-α also increases arginase activity leading to a decrease in NO production, having a vasoconstricting effect.[46] Patients suffering from IBD had elevated collagen production, associated with hyperplasia of smooth muscle cells, leading to arterial stiffening and endothelial dysfunction. Furthermore, the elevated blood levels of inflammatory mediators, IL-1 and TNF-α, trigger phenotypic alterations in vascular smooth muscle cells, which release matrix metalloproteinases that break down elastin and collagen fibers, producing stiffer fragments.[46] Also, these phenotypic changes in vascular smooth muscle cells lead to the increased expression of osteoblast markers, resulting in an elevated uptake of phosphate and production of apatite, medial calcification, and reduced vessel elasticity.[47] This abnormal collagen metabolism, secondary microvascular endothelial dysfunction, alteration of NO-mediated vasodilation, and deficiencies of vitamins and essential elements also contribute to myocardial fibrosis causing systolic and diastolic dysfunction leading to heart failure.[48] Myocardial fibrosis and impairs the intracellular calcium current from chronic inflammation often result in structural and electrical remodeling predisposing patients with IBD to atrial and ventricular arrhythmias and other conduction disturbances.[49] Chronic inflammation also leads to autonomic dysregulation (increased sympathetic tone and decreased parasympathetic tone), resulting in reduced heart rate variability and prolonged QT interval contributing to the development of arrhythmias.[50] Deficiencies of vitamins and essential elements and electrolyte disturbances (hypokalemia, hypocalcemia, and hypomagnesemia) among IBD patients are additional risk factors for ventricular arrhythmias.[6] Ischemia to the conduction system secondary to inflammation, vasculitis, and microvascular endothelial dysfunction causes atrioventricular conduction disturbances (complete atrioventricular block, second-degree or first-degree atrioventricular block.[49] Patients with IBD had an increased risk of aortic and mitral valvulopathies. Chronic systemic inflammation leads to increased levels of TNF-α which causes the thickening and shortening of the leaflets, resulting in regurgitation.[51] In addition, an overwhelming fibroblastic healing phenomenon

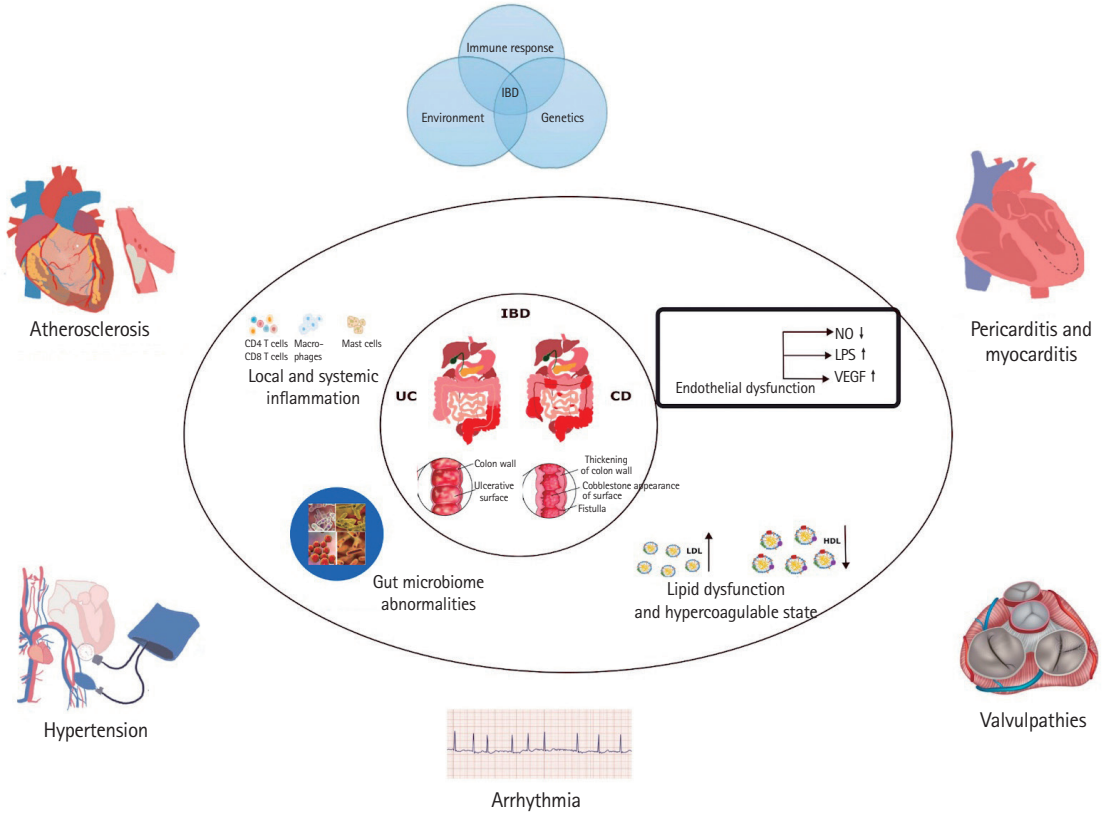

Fig. 3. Schematic presentation showing the link between inflammatory bowel disease (IBD) and cardiovascular disease. Elevated pro-inflammatory mediators promote cardiovascular events through endothelial dysfunction, intestinal dysbiosis, pro-inflammatory state, and lipid dysfunction. UC, ulcerative colitis; CD, Crohn's disease; NO, nitric oxide; LPS, lipoprotein lipase; VEGF, vascular endothelial growth factor; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

(as a subaortic bump on echocardiography) and a thickening of the aortic intima lead to ascending aortic aneurysm, thus predisposing to aortic regurgitation. The myxomatous degeneration (collagen deposition on the valve) results in a benign valve prolapse or mild regurgitation. Other changes secondary to the chronic inflammatory process include aortic aneurysm, ectasia, and coronary ostial stenosis.[6]

GENETIC LINKAGE BETWEEN CVD AND IBD

Several genes, like *NOD2, CDKN2B*, *Stromelysin*, and *ApoE* genetic polymorphism, have been implicated in cardiovascular and IBD pathogenesis due to common downstream signaling exerting the proinflammatory effect.[52] The frameshift mutation (*L1007fs*) and missense mutations (*R702W* and *G908R*) in the *NOD2* gene were the first well-documented mutations increasing susceptibility to CD.[53] NOD2 (previously known as CARD15) is pivotal in maintaining the balance between microbiome and host immune responses. An imbalance in this relationship results in dysbiosis, whereby pathogenic bacteria prevail on commensals, causing damage to the intestinal epithelial barrier and allowing bacterial invasion and inflammation.[54] Also, the prevalence of the Leu1007fsinsC polymorphism of the *NOD2* gene was significantly increased in CAD patients.[31] Various clinical studies have shown the role of NOD2 in inducing vascular inflammation and atherosclerosis by NOD2-mediated production of IL-6, IL-8, and IL-1β.[55] It has been localized in inflamed areas of atherosclerotic lesions and is overexpressed in endothelial cells delimiting the lumen of diseased vessels.[56]

Numerous genome-wide association studies (GWAS) conducted with both African American and European populations have confirmed the connection between the *NOD2* gene and CAD.[57] A population-based cohort study done for European populations suggested that *NOD2* mutations were seen in about 23.9% of CD patients and 9.6% of UC patients, and the prevalence of mutations was not directly linked to the incidence.[58] Other studies assessed the CARD15 (NOD2), R702W, G908R, and L1007fs variants in Dutch IBD patients and validated the link of G908R and L1008fs with CD susceptibility.[59] However, studies conducted in different parts of the world have given different data regarding this. For instance, a study was conducted to test Chinese IBD patients for the presence of allelic frequencies noted for Arg702Trp, Gly908Arg, and 3020insC SNP variants in the *NOD2/CARD15* gene. The results showed that these frequencies which were common in the Caucasian population were not noted in almost 200 Chinese CD, UC, and dyspepsia patients.[60] Moreover, a research study involving nearly 500 Japanese patients demonstrated that the *NOD2/CARD15* gene does not play a significant role in increasing the susceptibility to CD in Japanese populations.[61] Therefore, it can be stated that *NOD2* mutations are predominantly found in European populations, whereas Asian populations such as the Japanese and Chinese generally do not exhibit a high prevalence of these genetic variations.

The polymorphism in the leucine-rich repeat (LRR) domain of the *NOD2* gene is responsible for the clinical spectrum observed in CD. The LRR domain of CD-associated variants might be defective in detecting microbial elements and preventing NOD2 dimerization, often leading to the inappropriate activation of NF-κB in monocytes and affecting bacterial clearance and intestinal permeability. Thus, heterozygous individuals for NOD2 variants have a 2- to 4-fold increased risk of developing CD, whereas homozygous variants have an additional chance of 20- to 40-fold.[55] A recent study has shown that NOD2 aggravates myocardial ischemia/reperfusion injury by inducing cardiomyocyte apoptosis and inflammation through JNK (c-Jun N-terminal kinase), p38 MAPK (mitogen-activated protein kinase), and NF-κB signaling.[62] Due to the overlapping risk factors, genetic components, and underlying disease processes in both conditions, it is vital to promptly diagnose and treat IBD patients early in order to avert future cardiovascular complications.

DISCUSSION

IBD is characterized by persistent and recurring intestinal inflammation and presents symptoms like diarrhea, fatigue, abdominal pain, bloating, flatulence, and bloody stools.[63] Inflammation causes endothelial dysfunction responsible for various extraintestinal manifestations, including CVDs like atherosclerosis, pericarditis, and arrhythmias.[8] Inflammatory cells release pro-inflammatory cytokines, like TNF, CRP, and homocysteine, causing changes in glucose and lipid metabolism, which can cause plaque destabilization and development of ASCVD and increase in the stiffness of carotid-femoral arteries and the muscular arteries as shown by various studies.[42] Studies have shown that administering antibodies against TNF-α to patients with CD can improve their endothelial function. Further studies have demonstrated that anti-TNF-α antibody therapy can improve arterial stiffness and endothelial function in IBD patients. This highlights the importance of this inflammatory cy-

tokine in arterial dysfunction in IBD, which can potentially lead to CVD.[64] This increase in TNF has resulted from abnormal signaling from TLR receptors, as elevated levels of TLR2 and TLR4 have been observed in atherosclerotic plaques. In IBD patients, isolated monocytes showed elevated production and release of TNF-α after the addition of TLR2 agonists when compared to monocytes from healthy subjects. This indicates an increased expression/signaling of TLR2 in monocytes of IBD patients. While TLR4 polymorphism has been suggested to be associated with the disease state in IBD patients, this relationship has not been confirmed in other studies, and further research is required to establish it.[42,65] In addition, elevated homocysteine levels have increased thrombogenic potential. They are often related to various CVDs, particularly atherosclerosis, as shown by a study that the incidence of hyperhomocysteinemia is 4 to 5 fold higher in IBD patients than in control subjects.[42,66] Many studies have investigated the connection between CRP and CAD. CRP is overexpressed in atheromatous plaques and increases the uptake of LDL. A meta-analysis that included 160,309 individuals showed that patients with high serum CRP levels have a significantly higher risk of developing CAD compared to age- and sex-matched controls (one standard deviation increase in log CRP: relative risk, 1.63; $P<0.05$). Patients with IBD with elevated markers of systemic inflammation, such as CRP, may have a greater risk of developing CAD.[67]

The intestinal microbiota metabolizes dietary phosphatidylcholine to produce TMAO and elevated TMAO levels increase the risk of major adverse cardiovascular events. In addition, IBD patients are often at higher risk of CVD due to intestinal dysbiosis. Gut bacteria produce metabolites like phenol, indole derivative, and abnormal metabolism of phosphatidylcholine, resulting in increased production of TMAO that exacerbates atherosclerosis and increases the risk of adverse cardiovascular events.[41,43] A cohort study by Nikolaus et al.[68] in more than 500 patients with IBD found a negative connection between the levels of tryptophan in the blood and the activity of IBD. In addition, the study found that patients with active IBD had increased levels of tryptophan metabolites, particularly quinolinic acid, indicating high activity of tryptophan degradation. Tryptophan deficiency may contribute to the development or worsening of IBD. Further interventional clinical studies are required to determine if modifying the intestinal tryptophan pathways can impact the severity of IBD.[68] Another study by Tang et al.[69] showed that the intestinal microbiota produces TMAO through metabolizing dietary phosphatidylcholine, and elevated TMAO levels increase the risk of major adverse cardiovascular events.

Inflammation, immunomodulation, and gut dysbiosis account for the primary cause of CVD in patients suffering from IBD. Currently, there is a lack of evidence from interventional studies that define the optimal method for preventing ASCVD in patients with IBD. It is essential to screen all patients with IBD for established cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, and manage them aggressively. Patients with IBD need a deeper understanding of treatment targets for specific risk factors like hypertension, as they may experience marked volume losses during flares. It is also essential to frequently rescreen such risk factors in apparently cardiovascular-healthy patients.[70] Moreover, given the harmful effects of tobacco smoking, studies suggest that all patients with IBD should be encouraged to quit. Also, it is crucial to emphasize lifestyle modifications like regular exercise and stress and anxiety management.[71]

Patients with IBD should be discouraged from excessive intake of carbohydrates, fats, and refined sugars, a vital component of the Western diet, which often results in gut microbiota dysbiosis due to abnormal proliferation of *Prevotella, Bacteroides*, and *Escherichia coli*, leading to many inflammatory disorders, such as IBD.[2] On the contrary, these patients should be encouraged to consume the Mediterranean diet, lowering inflammatory markers and preventing carotid atherosclerosis, as shown by Chicco et al. in patients adhering to the Mediterranean diet regimen for 6 months, which has decreased inflammatory biomarker concentrations in their blood.[72,73] In addition, these patients should also include high fiber in their diet, which promotes the growth of *Bifidobacterium*, which can lead to remission in patients with UC.[3] In addition, individuals diagnosed with IBD should also be supplemented with vitamin D and sun exposure, as these patients are often more susceptible to vitamin D deficiency. Vitamin D is essential for reducing spasms in the smooth muscles of blood vessels and is especially significant for IBD patients who often experience endothelial cell dysfunction caused by circulating pro-inflammatory mediators.[74,75] Vitamin D can also reduce the likelihood of developing atherosclerosis by regulating the inflammatory response and reducing the expression of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1, and IL-8, as well as the accumulation of LDL in macrophages.[76] Additionally, vitamin D is crucial in regulating the renin-angiotensin-aldosterone system, modulating the inflammatory response, and influencing tissue calcium processes and modifications to the lipid and glucose profiles, which can help prevent CVD in patients

with IBD.[77] Supplementation with vitamin D at concentrations exceeding 30 ng/mL and sun exposure can also reduce LDL levels and increase HDL levels, thereby reducing the risk of cardiovascular conditions.[10] In conclusion, it is crucial to emphasize the importance of selecting appropriate medications, adhering to a healthy diet, supplementing with vitamin D, and promoting regular physical activity. Patients with IBD should incorporate the aforementioned elements into their diets to reduce disease activity and the risk of CVD, as these interventions help prevent ASCVD, improve the course of IBD, and reduce the risk of relapse.

Novel therapies like immunomodulators and biological agents have shown potential in reducing ASCVD risk in chronic inflammatory diseases like rheumatoid arthritis and human immunodeficiency virus infection. In psoriasis, biologic therapy for skin disease has been linked to reduced coronary inflammation, noncalcified plaque burden, and vascular inflammation, indicating that treating primary sources of inflammation is favorable for vascular health. In IBD, a recent French observational study involving 177,827 patients showed that using anti-TNF agents was associated with a decreased risk of acute arterial events, including coronary heart disease, cerebrovascular disease, and peripheral artery disease. Despite the large sample size and the use of complex multivariate models, these promising results need to be confirmed in experimental settings. Such studies will also provide valuable insights into the cardiovascular safety of these medications.[78]

Disease activity is a significant risk indicator for ASCVD. Therefore, optimizing the management of IBD in all patients, especially during active flares, is essential. The IBD-ASCVD connection raises the question of whether disease-modifying therapies, such as anti-inflammatory and immunomodulatory agents, can help reduce ASCVD risk.[79] A Danish cohort study found that using 5-aminosalicylates was associated with a lower risk of ischemic heart disease. Interestingly, this association was only present in patients taking corticosteroids, which were dose-dependent and used as a proxy for disease severity.[17]

The American College of Cardiology/American Heart Association and the European Society of Cardiology recommend considering chronic inflammatory conditions like IBD as risk enhancers or modifiers and using chronic HMG-CoA reductase inhibitors (statin) therapy among patients at borderline or intermediate risk as these have been found to have immunomodulatory and anti-inflammatory effects in addition to lowering serum lipids. Specifically, their anti-inflammatory action is believed to be due to their interference with endothelial adhesion and trans-endothelial migration of leukocytes to sites of inflammation.[67]

A retrospective cohort study has shown that atorvastatin may benefit patients with IBD. The study found that atorvastatin was associated with an 18% reduction in the initiation of oral steroids (HR, 0.82; $P=0.05$) and a 25% decrease in the use of oral steroids in patients with UC (HR, 0.75; $P=0.05$). There were also trends towards a decrease in the use of oral steroids in CD, as well as a reduction in anti-TNF therapy, abdominal surgeries, and hospitalizations in IBD.[80]

Furthermore, a recent pilot study demonstrated that patients with CD given 80 mg of atorvastatin once daily for 13 weeks had reduced CRP levels and a subjective decrease in symptoms. Therefore, atorvastatin therapy may help reduce inflammation in patients with IBD, and its protective effects should be studied further.[81]

In addition, angiotensin-converting enzyme (ACE) inhibitors, commonly prescribed for hypertension, postmyocardial infarction, and congestive heart failure, may also have a role in managing IBD. ACE inhibitors inhibit the renin aldosterone-angiotensin system, downregulate inflammatory cytokines, and prevent fibrosis with subsequent ventricular remodeling. Studies on patients with IBD have shown that mucosal angiotensin I and angiotensin II were increased, which supports the theory that angiotensin peptides mediate inflammation and fibrosis in IBD.[67]

Patients with chronic inflammatory conditions like IBD have an increased risk of plaque buildup and high-risk plaque features. It is worth evaluating whether identifying such patients using advanced techniques can improve the selection of candidates for intensive CVD prevention interventions, beyond traditional risk factors and intensive management.

CONCLUSION

IBD is a widespread inflammatory disease that not only causes relapsing inflammation of the gastrointestinal tract but has been shown to increase extraintestinal manifestations, including cardiovascular complications. With 6.8 million people worldwide currently impacted, along with more than 1 million Americans, the need to better understand the association between IBD and cardiovascular complications is crucial to improve cardiovascular outcomes in these individuals. The findings highlight that IBD's association with CVD does not follow a single pathway; rather, it is multifold. On the one hand, chronic inflammation has been shown to lead to atherosclerosis: a pro-

cess that results from an increase in immune and inflammatory cells and, ultimately, proinflammatory cytokines. The changes that inflammation has on the metabolism of lipids are documented and correlated to an increased risk of ASCVD due to increased LDL, triglycerides, insulin resistance, and decreased HDL. In addition, IBD can also lead to damage to collagen metabolism and dysregulation of NO-mediated vasodilation, which ultimately causes abnormal blood pressure regulation. This review also emphasizes the detrimental effect of vitamins, essential elements, and electrolyte disturbances (hypokalemia, hypocalcemia, and hypomagnesemia) among IBD patients, which have the potential to result in ventricular arrhythmias. The combination of abnormal collagen metabolism, alteration of NO-mediated vasodilation, and deficiencies of vitamins and essential elements can lead to myocardial fibrosis, causing systolic and diastolic dysfunction and, eventually, heart failure. Several studies published over the past decade report the increased incidence of cardiac manifestations in patients with IBD compared to patients without IBD. Therefore, it is essential to make lifestyle modifications like smoking cessation, dietary changes, and increasing physical activity with adherence to medication to mitigate the risk of developing CVD in patients with IBD.

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