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Review Article

Metabolic Disorders and Inflammatory Bowel Diseases

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Inflammatory bowel disease (IBD) is characterized by chronic immune-mediated intestinal inflammation, presenting with a spectrum of metabolic disorders as well as intestinal and extraintestinal manifestations. Lifestyle factors, genetic predisposition, immune dysfunction, and gut bacteria composition contribute to the development of IBD. Several comorbidities, including cardiovascular diseases, thrombosis, and metabolic disorders, have been associated with IBD. Therefore, metabolic disorders, including nonalcoholic fatty liver disease, type 2 diabetes mellitus, and obesity have become the focus of attention in patients with IBD. Identifying and managing these conditions can significantly influence patient outcomes and enhance overall management. Therefore, this review aimed to elucidate the current understanding of relevant and emerging metabolic comorbidities and extraintestinal manifestations associated with IBD and their clinical significance. **(Gut Liver, 2025;19:307-317)**

Key Words: Inflammatory bowel diseases; Metabolic diseases; Ulcerative colitis; Crohn disease

INTRODUCTION

Inflammatory bowel disease (IBD) is an intestinal immune-mediated disease characterized by chronic relapsing inflammation, encompassing conditions such as ulcerative colitis (UC) and Crohn's disease (CD).[1] Additionally, various clinical manifestations throughout the body are intertwined with significant comorbidities associated with disease prognosis.[2] IBD pathophysiology is intricate, involving many factors, including genetics, environment, gut microbial composition, and immune system dynamics.[3,4] The metabolic nature of gut inflammation in IBD shares distinct parallels with the inflammatory state observed in metabolic diseases. Epidemiological studies have indicated that the incidence of IBD increases with an aging patient population, alongside metabolic disorders and extraintestinal manifestations.[5] The association between IBD and metabolic syndrome is multifaceted and warrants comprehensive exploration. Metabolic syndrome, characterized by obesity, dyslipidemia, hypertension, and insulin resistance, heightens the risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM).

Metabolic inflammation, a chronic low-grade inflammation recognized as a hallmark of many metabolic disorders, arises from many non-infectious factors, particularly excess dietary lipids, impacting organs involved in lipid metabolism, such as the liver, muscle, and adipose tissues.[6,7] Epidemiological studies have consistently demonstrated a correlation between metabolic syndrome and IBD, indicating shared pathogenic mechanisms. IBD and metabolic syndrome exhibit chronic low-grade inflammation and dysregulated lipid metabolism.[8,9] This convergence suggests potential commonalities in their etiology, although the precise mechanisms have not been fully elucidated. Metabolic syndrome in patients with IBD can exacerbate inflammation, leading to increased disease severity and a higher risk of extraintestinal manifestations. Understanding this interplay is crucial for optimizing patient care and outcomes.

Recent microbiome studies are moving beyond merely describing microbial community structures and their disease associations. These studies are progressing toward understanding the fundamental causative roles of gut bacteria in the pathogenesis of complex chronic metabolic dis-

orders.[4,10] Despite these advances, significant gaps remain in our understanding of the relationship between IBD and metabolic syndrome. Further research is required to clarify the underlying mechanisms and determine optimal management strategies for patients affected by these conditions.

In this review, we aimed to discuss the most relevant and emerging metabolic disorders and extraintestinal manifestations that are underdiagnosed in patients with IBD. We also aimed to facilitate the early detection, assessment, and management of these comorbidities, enabling the prediction of disease outcomes and ultimately improving the quality of life of patients with IBD.

METABOLIC SYNDROME IN PATIENTS WITH IBD: NAFLD AND MAFLD

Metabolic syndrome is a cluster of health conditions that exacerbate the risk of heart disease, stroke, and diabetes mellitus (DM) (Table 1). These conditions encompass excess abdominal obesity, elevated blood pressure, high blood sugar levels, increased triglyceride levels, and reduced levels of high-density lipoprotein.[11-15] The prevalence of metabolic syndrome in patients with IBD is notable and closely related to each other.[16,17]

Nonalcoholic fatty liver disease (NAFLD) is diagnosed histologically by hepatic fat accumulation in individuals without excessive alcohol intake. Metabolic dysfunction-associated fatty liver disease (MAFLD), a term that emerged in 2020, encompasses metabolic dysregulation more comprehensively. MAFLD is determined by the presence of hepatic steatosis along with at least one of three features: T2DM, obesity, or metabolic dysregulation, comprising at least two metabolic risk abnormalities between waist circumference, blood pressure, plasma triglycerides, plasma high-density lipoprotein cholesterol, prediabetes, glycosylated hemoglobin, insulin resistance and high-sensitivity C-reactive protein levels.[18] MAFLD pathogenesis is underpinned by the synergistic interplay of metabolic disruptions and pro-inflammatory processes commonly associated with conditions such as obesity and insulin resistance. MAFLD is frequently characterized by a progressive nature. The prevalence of MAFLD in patients with IBD is estimated to range from 8% to 88%.[19,20] This discrepancy may be because of the heterogeneity of the diagnostic methods and cutoff values for the selected study population. The chronic inflammatory burden of IBD serves as a potential risk factor for advanced liver fibrosis regardless of the typical risk factors associated with MAFLD.[21] Alterations in gut dysbiosis and bacterial diversity have been linked to several chronic liver diseases.[22] A systematic review followed by a subsequent meta-analysis revealed that the prevalence of NAFLD among patients with IBD (32%) is significantly higher than that in the general population (25.2%; $p<0.001$).[23] Previous studies have proposed that NAFLD development in patients with IBD may be influenced by characteristics associated with IBD, including the use of hepatotoxic medications, more severe disease activity, longer disease duration, higher inflammatory burden, and history of intestinal surgery.[24,25] A previous study revealed that hepatic steatosis, rather than fibrosis burden, independently correlated with an elevated risk of clinical relapse in patients with UC and CD.[26] A nationwide analysis in the United States demonstrated that NAFLD is associated with worse hospitalization outcomes in patients with CD and UC, after adjusting for metabolic factors.[27] Another study reported that hepatic steatosis was independently associated with an increased risk of clinical relapse in patients with IBD.[26,28] To mitigate fibrotic burden and lower the incidence of clinical relapse in patients with IBD, incorporating the monitoring of hepatic steatosis and fibrosis using easy-to-use, noninvasive surrogate tools based on several clinical parameters is crucial. The pathogenesis of NAFLD in patients with IBD may be influenced by disease-specific risk factors related to chronic inflammation.[29] The predictors of NAFLD include disease duration and severity, corticosteroid use, small bowel surgery, and changes in gut microbiota.[29] Previous studies have shown differences between CD and UC in patients with NAFLD, while hepatic steatosis independently raised the risk of clinical relapse in patients with CD.[26] In general, CD mainly involves the distal ileum causing reduced intestinal reabsorption of bile while increasing enterohepatic circulation, resulting in the formation bile supersaturated

Table 1. Metabolic Syndrome Encompasses Conditions That Increase the Risk of Heart Disease, Stroke, and Diabetes Mellitus

Author	Metabolic syndrome component	Health impact
Powell-Wiley *et al.*[11]	Excess abdominal fat	Increases risk of heart disease
Gorelick *et al.*[12]	High blood pressure	Raises risk of stroke
Marott *et al.*[13]	Elevated fasting blood sugar	Leads to diabetes
Miller *et al.*[14]	High triglyceride levels	Contributes to heart disease
Liu *et al.*[15]	Low HDL cholesterol levels	Enhances risk of heart disease

HDL, high-density lipoprotein.

with cholesterol,[30] which might be associated with the higher risk of NAFLD development. The duration of IBD diagnosis is thought to be another independent factor in the development of NAFLD.[31] Because patients with CD are usually diagnosed at a young age, the duration of the disease is prolonged, and consequently, they are exposed to an inflammatory situation over a longer period of time compared to those with UC. This prolonged disease may also alter the gut microbiome and increase the likelihood of using hepatotoxic drugs. Additionally, maintaining sobriety, controlling weight, and engaging in aerobic exercise at least three times a week are important to reduce liver fat accumulation and manage NAFLD and MAFLD.

OBESITY IN PATIENTS WITH IBD

Obesity, characterized by excessive fat accumulation, is defined as a body mass index (BMI) greater than 25 kg/m^2.[32] It is commonly associated with a Westernized lifestyle, marked by sedentary behavior and excessive consumption of calories from diets rich in refined grains and unhealthy fats.[33] Epidemiological studies have discovered that 15% to 40% of individuals with IBD are obese.[34,35] A pooled analysis of five prospective cohort studies revealed that obesity is associated with an increased risk of CD but not UC. For every 5 kg/m^2 increase in baseline BMI, the risk of CD increased by 16%. Similarly, each 5 kg/m^2 increase in BMI during early adulthood (ages 18 to 20) was associated with a 22% increased risk of CD. However, no correlation was observed between UC risk and indicators of obesity.[36] A nationwide cohort study of 10 million individuals using the Korea National Health Insurance Service database also showed that an increase in baseline waist circumference was linked to an increased risk of developing CD but not UC.[37] An increasing association is being recognized between obesity and IBD, mainly because of its overall pro-inflammatory effects on both conditions. Obesity is a chronic low-grade systemic inflammation condition that entails increased pro-inflammatory cytokine secretion from adipose tissue and the infiltration of leukocytes, such as macrophages, into adipose tissue. The pro-inflammatory effects of cytokines, such as interleukin (IL)-7 and IL-34, enhance adipogenesis.[38] The mechanisms by which obesity is related to CD involve the secretion of pro-inflammatory cytokines or adipokines released by adipocytes. Additionally, adipocyte hypertrophy in obesity triggers inflammation by releasing inflammatory molecules such as tumor necrosis factor (TNF)-α and C-reactive protein. Patients with IBD often have elevated levels of these markers, which can be countered by anti-TNF therapies against the pathogenic effects of TNF-α.[36]

Early research on humans identified a unique characteristic of the gut microbiota associated with obesity. Obesity alters the composition of major gut bacterial divisions, *Bacteroidetes* and *Firmicutes*, thereby affecting the metabolic capabilities of the gut microbiota. Consequently, the microbiome of individuals with obesity demonstrates an increased capacity to obtain energy from the diet.[39] Similar to IBD, obesity is associated with alterations in gut microbiota composition, characterized by decreased diversity and changes in bacterial abundance, notably an increase in *Firmicutes* and a decrease in *Bacteroidetes*.[10,40] Key species including *Escherichia coli*, *Oxalobacter formigenes*, and *Actinomyces graevenitzii* have previously been associated with IBD.[41] In patients with IBD who are also obese, several key genera and species are notably changed. The genus *Firmicutes*, including *Clostridia* and *Lactobacillus*, is often increased, impacting gut metabolism.[42] *Roseburia*, known for short-chain fatty acid production, may be elevated in obesity, but varies in IBD. *Faecalibacterium prausnitzii*, which is important for gut health, is generally reduced in both conditions.[42] Additionally, *Akkermansia*, specifically *Akkermansia muciniphila*, is linked to mucosal health; its levels may be altered in IBD and obesity, indicating changes in mucosal barrier function.[43] These genera and species illustrate the intricate relationship between microbiota alterations and disease progression in obesity and IBD.

Substantial weight reduction affects the expression of IL-1F members in adipose and liver tissue, potentially playing a role in modulating insulin resistance and inflammation.[44] When weight loss is induced, a significant decrease in inflammatory cytokines in the liver or subcutaneous fat is observed. Thus, maintaining a BMI within the range of 18.5 to 22.9 kg/m^2 in patients with IBD and promoting weight loss in those with obesity may alleviate the risk of poor outcomes, which requires further clarification.

DM IN PATIENTS WITH IBD

DM is a chronic metabolic disorder characterized by elevated blood glucose levels resulting from insulin deficiency or resistance. DM leads to impaired glucose utilization and eventual damage to various organs.[45] DM prevalence in patients with IBD remains controversial. A recent epidemiologic study in the United States showed no significant association between DM and IBD.[46] However, a nationwide population-based cohort study conducted in Denmark revealed that patients with UC and CD exhibited a higher risk of developing T2DM than did those without the conditions, with an incidence ratio of 1.54 (95% confi-

dence interval, 1.49 to 1.60).[47]

The gut microbiome is a link between DM and IBD. Research since 2012 has revealed alterations in the microbiome of individuals diagnosed with DM. Microbiome risk profiles observed in DM and IBD show significant overlap, suggesting an association between the two conditions owing to microbiome changes.[48] Differences in bacterial species and metabolic gene cluster profiles have been used to identify diabetes status in individuals with normal glucose tolerance or T2DM. Several studies have provided evidence of a causal correlation between specific members of the intestinal microbiota and the pathogenesis of T2DM. A study utilizing prospective natural history data discovered higher occurrences of inflammatory biomarkers, such as C-reactive protein and erythrocyte sedimentation rate, which are commonly associated with heightened severity of IBD, in patients with T2DM. Additionally, the hospitalization rate was higher in IBD patients with DM than in those without DM.[49] Furthermore, differences in microbiome composition have been associated with insulin resistance and development of diabetes. A cross-sectional study involving 2,166 participants from the Rotterdam and LifeLines-DEEP cohorts found that higher microbiome α diversity and a greater abundance of butyrate-producing gut bacteria were linked to a lower prevalence of T2DM and reduced insulin resistance among individuals without diabetes.[50] Recent efforts to manage diabetes through microbiome modulation have shown promise. A phase 2 placebo-controlled trial with obese patients with metabolic syndrome demonstrated that supplementation with a low fermentable fiber supplement and capsules containing fecal material from healthy donors improved insulin sensitivity.[51] This result suggests that non-invasive fecal microbiota transplantation might offer a viable alternative to more invasive methods.

The mechanism contributing to elevated inflammation levels in patients with DM is linked to higher levels of circulating inflammatory cytokines, including TNF-α, which acts as a key molecule in peripheral insulin resistance, and IL-1β, which is involved in pancreatic β-cell damage.[52,53] Moreover, multiple cytokines, including TNF-α, IL-1β, and IL-6, play a role in inflammation and serve as common therapeutic targets in patients with IBD.[49] Regular blood sugar monitoring should be considered for the early detection of diabetes in patients with IBD, particularly among younger individuals. Additionally, effective control of blood sugar levels through dietary adjustments and lifestyle modifications is crucial for managing clinical relapse in these patients.

CVDs IN PATIENTS WITH IBD

CVDs are conditions affecting the heart or blood vessels, often related to atherosclerosis. These diseases include coronary heart disease, cerebrovascular disease, and peripheral arterial disease.[54] The number of older patients with IBD is increasing, along with a rise in the incidence of comorbidities.[55] A nationwide Danish cohort study indicated an increased risk of ischemic heart disease, including myocardial infarction, within the initial year following an IBD diagnosis in patients compared with those without IBD.[56] The risks of myocardial infarction, stroke, and cardiovascular mortality were significantly higher during periods of IBD activity, including flares and persistent symptoms, compared with periods of remission.[57] Among patients with IBD, the occurrence rates for CVD, heart failure, and stroke events were 1.95%, 5.49%, and 0.95%, respectively.[58] IBD is associated with a higher risk of CVDs, particularly in women and young adults.[58,59] A U.K. study revealed that patients with CD aged under 50 years had a greater risk of ischemic stroke than did those without CD,[60] and women aged under 40 years with IBD had a significantly higher stroke risk than did those without CD.[61] IBD is associated with coagulopathy owing to its nature. It tends to elevate the risk of thrombosis and impacts cardiovascular health by increasing platelet activation and aggregation, decreasing plasminolysis, and altering endothelial function.[62]

VENOUS THROMBOSIS IN PATIENTS WITH IBD

Venous thrombosis in patients with IBD is not directly associated with metabolic syndrome; however, it similarly contributes to vascular complications and significantly influences the prognosis of these patients.[63,64] Patients with IBD have a 3-fold greater risk of experiencing deep vein thrombosis or pulmonary embolism than the general population. Disease activity may also contribute to this elevated risk of thromboembolism.[62] The incidence of venous thromboembolism (VTE) within the IBD cohort is 7.6%, which is remarkably higher than the incidence in controls.[65,66] The two major risk factors for venous thrombosis in patients with IBD are disease activity and hospitalization. Cohort studies have indicated that 71% of VTE events occur in patients with active disease.[67,68]

In IBD, thrombosis typically arises from three primary mechanisms: an escalation in the number and activation level of platelets, activation of the coagulation pathway, and elevation in clot density along with prolonged clot lysis

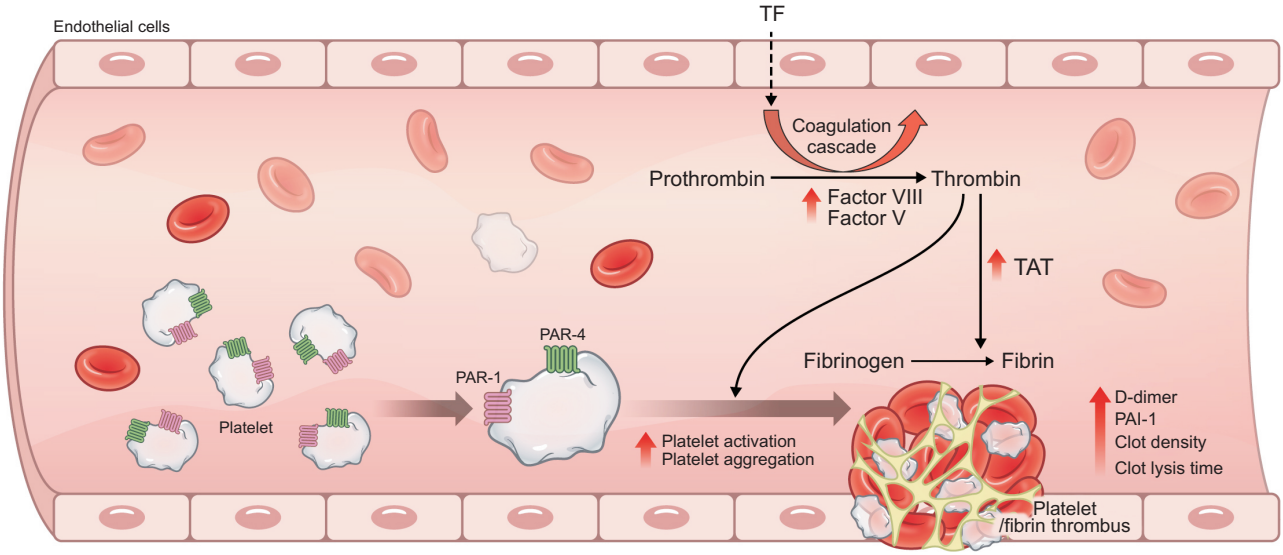

Fig. 1. Key mechanisms of thrombosis in inflammatory bowel disease: platelet activation, coagulation pathway activation, and increased clot density. TF, tissue factor; TAT, thrombin-antithrombin complex; PAR, protease-activated receptor; PAI, plasminogen activator inhibitor.

time (Fig. 1).[69,70] VTE represents a multifactorial threshold condition with cumulative risk factors. Considering the daily risks faced by patients with IBD, low-risk factors include advanced age, obesity, and extended air travel. Moderate-risk factors include smoking, malignancy, and oral contraceptive use. High-risk factors include hospitalization, surgical procedures, and a history of embolism.[71] The risk of VTE is elevated during hospitalization, with a 6-fold higher risk compared with ambulatory patients with IBD.[68] Hospitalization confers a substantial risk of VTE; however, this risk persists beyond discharge. Particularly within the initial 10 days post-discharge, a heightened susceptibility to VTE recurrence occurs, a phenomenon implicated in readmission. This risk is crucial in individuals with a history of VTE, severe disease activity, or comorbidities, necessitating continued vigilance for VTE post-discharge.[72,73]

Major risk factors of VTE include active malignancy, recent surgery with general anesthesia (<3 months, >30 minutes), lower limb trauma, and high-risk thrombophilia. Minor risk factors include recent surgery with general anesthesia (<3 months, <30 minutes), venous catheter placement, advanced age (>65 years), pregnancy, post-partum period, lower-risk thrombophilia, a history of VTE, and obesity. Thromboprophylaxis through anticoagulation is advised for all hospitalized patients to mitigate the risk of VTE in patients with IBD. Given the sustained vulnerability to VTE post-discharge, ongoing consideration of anticoagulation is warranted. Therefore, low-molecular-weight heparins are preferred over unfractionated heparin.[74]

CVDs AND VENOUS THROMBOSIS ASSOCIATED WITH TREATMENT OF IBD

The development of new drugs, including corticosteroids and biologics, could impact CVD and thromboembolism risk in patients with IBD. Several studies have suggested that patients with IBD who receive corticosteroids have a high risk of cardiometabolic abnormalities and CVD owing to the interruption of physiological metabolic processes.[59,75] The ORAL (Oral Rheumatoid Arthritis Trial) Surveillance study, an open-label, phase 3/4 post-marketing non-inferiority trial, assessed the cardiovascular and cancer risks associated with tofacitinib in patients with rheumatoid arthritis (RA).[76] Compared with TNF inhibitors, tofacitinib was associated with a higher incidence of major adverse cardiovascular events (MACE) and malignancies in patients with RA aged 50 years or older who had at least one additional cardiovascular risk factor.

In subgroup analyses, the comparison between anti-TNF treatment and tofacitinib did not reveal a significant difference among non-smoking patients under 65 years of age. However, for individuals over 65 years of age, an increase in the risk of MACE associated with tofacitinib was observed.[76] Systematic reviews and meta-analyses have suggested that Janus kinase (JAK) inhibitors do not increase the risk of MACE in patients with IBD, unlike in patients with RA.[77] The final analysis of the open-label OCTAVE (Oral Clinical Trials for tofAcitinib in ulceratiVE colitis) study, which evaluated the long-term safety and efficacy of tofacitinib in treating UC, revealed that the incidence rate of MACE remained low at 0.4%.[78] Compared with the ORAL Surveillance study, the OCTAVE trial

revealed that individuals with lower underlying cardiovascular risk tend to have a lower occurrence of MACE. Differences in outcomes between these two studies could be attributed to variations in the baseline characteristics of the patient groups and individual patient risk factors.[79] Another systematic review and meta-analysis regarding tofacitinib in patients with UC revealed no MACE among real-world patients.[80] Further studies are warranted to draw concrete conclusions about the cardiovascular risk of JAK inhibitors in patients with IBD.

A recent analysis of upadacitinib, a selective JAK inhibitor, showed no reports of MACE during the induction phase, with MACE occurrences only noted in the maintenance phase among patients receiving a placebo.[81] Considering previous reports that MACE is associated with tofacitinib, upadacitinib might be a safer option. However, further investigations are warranted to determine whether JAK inhibitors inherently elevate the risk of MACE.

Regarding the cardiovascular risk associated with JAK inhibitors in IBD, the fundamental differences between RA and IBD, in terms of the nature and the relative prevalence of comorbidities and cardiovascular risk profiles in patients with IBD, must be recognized. Therefore, the concerns highlighted by the ORAL Surveillance study may not necessarily translate to significant apprehension regarding the use of JAK inhibitors in IBD, especially given the relatively low cardiovascular risk burden in the patient population.[81] Further studies are required to fully understand the relationship between JAK inhibitors and cardiovascular risk in patients with IBD.

Despite these findings, the Food and Drug Administration, and European Medicines Agency have issued cautionary recommendations regarding the use of all JAK inhibitors based on ORAL Surveillance study results. These agencies advise careful consideration when prescribing these medications and suggest their use only when alternative treatments are unavailable for high-risk patients. Accordingly, in Korea, the use of JAK inhibitors can be considered when alternative treatments are unavailable for certain high-risk groups, such as individuals aged 65 years or older, those at high risk for CVD, and those with malignant tumors.

In pharmacotherapy, VTE remains a concern, and corticosteroids are recognized as elevating the risk level. Conversely, anti-TNF treatments have been documented to reduce VTE risk by approximately 5-fold.[82,83] In RA, the ORAL surveillance study revealed an increased risk of venous thrombosis, including pulmonary embolism, deep vein thrombosis, and VTE, associated with tofacitinib use. However, in a study of patients with UC, only five cases of VTE were reported among 2,000 patients using tofacitinib, all of whom had pre-existing VTE risk factors. This work suggests that the actual risk in IBD may not be significantly elevated after tofacitinib use, similar to findings observed in MACE.[76] In a maintenance study utilizing upadacitinib, a selective JAK inhibitor, two cases of VTE were observed among 154 patients.[81] In 2021, guidelines concerning thrombotic events in patients with IBD were published stating that using tofacitinib in UC does not significantly increase the risk of VTE. Nonetheless, assessing VTE risk factors before initiating tofacitinib treatment and using the lowest effective dose possible are recommended. Screening for VTE risk factors early to prevent VTE is advisable. Hence, the selection of pharmacological treatment should be meticulously tailored to the patient's specific underlying conditions and risk factors.

DIET IN PATIENTS WITH IBD

Diet is not a disease; however, metabolic syndrome and IBD are closely related to food intake.[84] *In vivo* experiments have revealed that excessive consumption of simple carbohydrates, polyunsaturated fatty acids, and dietary additives in Western diets causes intestinal inflammation in mice. Epidemiological studies have also indicated that adopting a Westernized diet may increase the risk of developing IBD and obesity-related disorders. The inflammatory nature of such a diet in IBD supports the idea of diet-induced metabolic gut inflammation.[5] A high-fat Western diet reduces intestinal epithelial function in the small intestine, and excessive consumption of polyunsaturated fatty acids in a Western diet causes acute enteritis in CEABAC10 transgenic mice.[5] Consuming excessive amounts of artificial sweeteners or processed foods can disrupt the balance of gut bacteria and compromise the integrity of the gut barrier. This disturbance in gut dysbiosis triggers inflammatory pathways, causing recurrent instances of acute gut injury and compromised healing, ultimately resulting in chronic inflammation.[5] Diet affects the intestines and causes other systemic disorders associated with metabolic inflammation. Kawano *et al.*[85] investigated the mechanisms by which dietary sugars are associated with gut inflammation and metabolic syndrome. When consuming a regular diet, Th17 cells derived from the microbiome play a role in suppressing fat absorption. Even with high fat intake, effective Th17 cell function can help reduce fat absorption, potentially lowering the risk of metabolic syndrome. However, a Western diet high in sugar and fat can disturb the balance of gut microbiota and impair Th17 cell activity. When high amounts of fat enter the body, the defense mechanism may not operate effectively, leading to the

direct absorption of ingested fat and potentially contributing to the development of metabolic syndrome.[85] High dietary sugar levels induce inflammation by stimulating the inflammatory pathway, and added sugar intensifies early metabolic disease by diminishing protective Th17 immunity, consequently fostering intestinal lipid absorption and contributing to obesity.[86]

Probiotics, live beneficial bacteria found in certain foods or supplements, play a crucial role in managing IBD. They can help restore the balance of disrupted gut microbiota, potentially reducing intestinal inflammation and alleviating symptoms, such as diarrhea and abdominal pain.[87] On the other hand, prebiotics are non-digestible fibers that stimulate the growth and activity of beneficial gut bacteria. Their role in IBD involves supporting the proliferation of these beneficial bacteria, thereby promoting a healthier gut environment. Prebiotics can enhance overall digestive and immune function, which are crucial for maintaining gut health.[88] Including both probiotics and prebiotics in the care plan for patients with IBD may provide additional therapeutic benefits; patients are encouraged to consult with their healthcare professional to tailor these interventions to their specific needs. According to the 2017 guidelines from the European Crohn's and Colitis Organisation, *E. coli* Nissle 1917 is the only probiotic strain to have shown limited efficacy in UC. The guidelines state that there is currently no substantial evidence supporting the efficacy of any other probiotic strains.[89] Similarly, the 2020 guidelines from the American Gastroenterological Association indicate that the evidence for the effectiveness of probiotics in IBD remains very limited due to small sample sizes, patient variability, and heterogeneity in study methods and probiotic strains. Therefore, the American Gastroenterological Association is withholding recommendations for the use of probiotics in IBD at this time.[90]

The Crohn's disease exclusion diet is designed to exclude or limit foods that negatively impact gut microbiota or alter gut barrier function. It differentiates between "allowed foods" and "restricted foods" to induce remission, and is divided into three phases: phase 1 and phase 2 (each lasting 6 weeks), and phase 3 (post-remission). Early phases limit permissible foods to items like white rice, preservative-free rice noodles, specific fruits, and certain proteins, while wheat, yeast, corn, various snacks, processed products, and most fruits and vegetables are not listed as permissible. Crohn's disease exclusion diet is proposed as a treatment method to induce remission in patients with mild to moderately active CD. The association between diet with IBD and metabolic syndrome is summarized in Fig. 2.

CONCLUSIONS

The mechanisms underlying chronic inflammation in metabolic disorders are intricate and multifaceted. Chronic inflammatory burden can lead to metabolic disorders, including NAFLD and MAFLD, through metabolic dysregulation. Conversely, metabolic syndrome can negatively impact the prognosis of IBD. Obesity-induced inflamma-

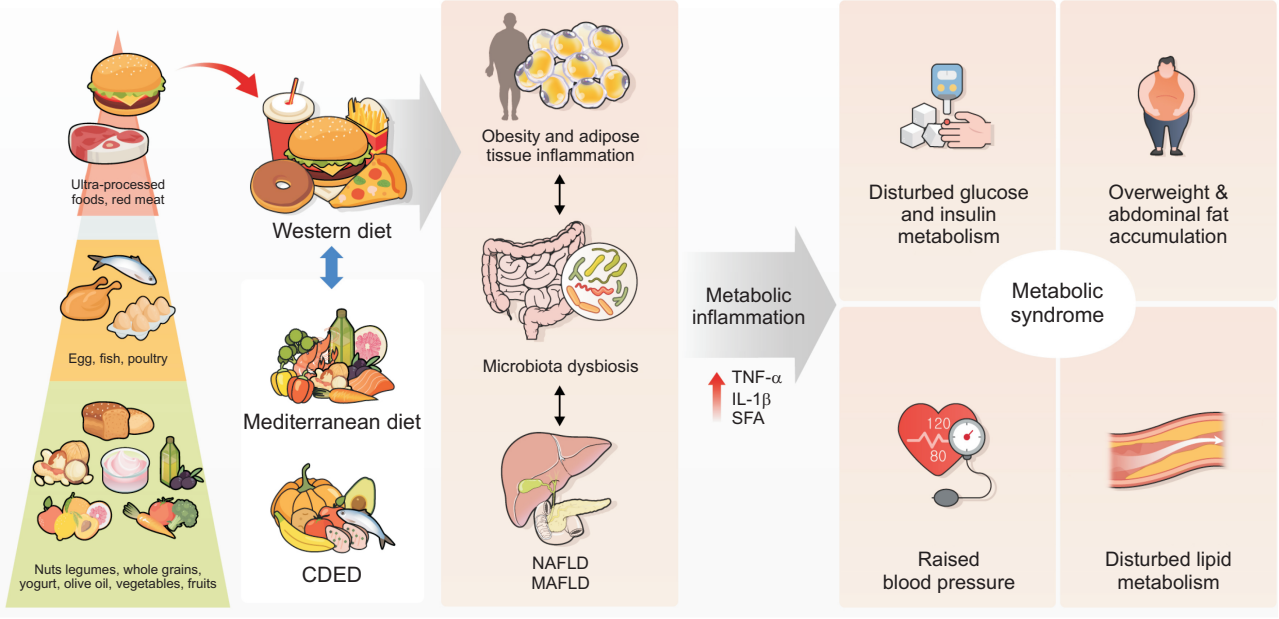

Fig. 2. Impact of diets on metabolic syndrome in inflammatory bowel disease. CDED, Crohn's disease exclusion diet; NAFLD, nonalcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; TNF, tumor necrosis factor; IL, interleukin; SFA, short-chain fatty acid.

tory cytokines may increase IBD risk, and changes in the microbiome risk profile indicative of microbial dysbiosis in patients with IBD suggest an association of Western-style diet with DM, as well as with NAFLD. Given their association with the clinical outcomes of patients with IBD, vigilance about these conditions is warranted, recognizing that their impact extends beyond mere co-occurrence to influencing the outcomes of patients with IBD. Moreover, in patients with severe disease activity in IBD, vigilance is also warranted, given that activation of coagulation pathways may increase thrombotic and cardiovascular risks. Utilizing anticoagulants in high-risk patients with comorbidities should be considered without delay. Beyond gut symptoms, ranging from mild to severe, which can cause permanent damage, IBD can affect various organs in patients with IBD. Hence, early identification of metabolic syndrome in patients with IBD is imperative to facilitate comprehensive treatment strategies. Finally, a multidisciplinary approach and follow-up involving experts in the field are essential to effectively resolve these conditions.

CONFLICTS OF INTEREST

J.H.C. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Study concept and design: H.K.H., J.H.C. Data acquisition: H.K.H., J.H.C. Data analysis and interpretation: H.K.H., J.H.C. Drafting of the manuscript: H.K.H., J.H.C. Critical revision of the manuscript for important intellectual content: H.K.H., J.H.C. Statistical analysis: H.K.H., J.H.C. Administrative, technical, or material support; H.K.H., J.H.C. Study supervision: J.H.C. Approval of final manuscript: all authors.

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