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Metabolic and cardiovascular disorders in patients with inflammatory bowel diseases

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Abstract

Nonspecific inflammatory bowel diseases (IBD) - ulcerative colitis (UC), and Crohn's disease (CD) have a complex impact on patients' health. IBD often coexists with other immune-related conditions like type 1 diabetes. IBD patients are also susceptible to metabolic issues, including dyslipidemia, fatty liver, type 2 diabetes, obesity, and ischemic heart disease, primarily due to chronic inflammation disrupting metabolic processes. IBD treatment can also affect body weight and metabolism, contributing to these problems. These disorders may arise from adverse changes in gut microbiota, chronic inflammation, and the activation of adipokines, cytokines, and reactive oxygen species. CD and UC can increase blood clotting, raising the risk of cardiovascular issues. IBD management includes anti-inflammatory and immunosuppressive drugs to control inflammation. However, addressing comorbidities and promoting tailored lifestyle and dietary changes is essential for IBD care, even though it may affect metabolic health. *(Farm Współ 2024; 17: 159-164) doi: 10.53139/FW.20241718*

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Introduction

The incidence of nonspecific enteritis, including ulcerative colitis and Crohn's (CD) disease, has been steadily increasing worldwide in recent decades. The peak incidence of these individuals occurs between the second and fourth decades of life. The incidence of Crohn's disease and ulcerative colitis (UC) is similar in both sexes. The incidence is highest in Western areas among white and Jewish people. Recently, Asian and Hispanic populations have also been increasing. UC and CD are believed to result from interactions between environmental factors and genetic tendencies. The growing population of people suffering from chronic enteritis, dietary restrictions used in this disease, and the use of certain drugs may significantly increase the frequency and number of metabolic diseases diagnosed in this population.

Inflammatory bowel diseases and type 1 and type 2 diabetes

Type 1 diabetes (type 1 diabetes mellitus, T1D) as Crohn's disease and ulcerative colitis belong to chronic autoimmune diseases. It has been proven that predisposition to some inflammatory diseases like ulcerative colitis and Crohn's disease is inherited. However, Andersen et al. found no correlation between the inheritance of diabetes and the development of inflammatory bowel diseases [1]. Other research proves that the protein tyrosine phosphatase genes (PTPN2) and (PTPN22) cause the possibility of developing many autoimmune diseases, including Crohn's disease and type 1 diabetes. Genes such as *ORMDL3* and *IL-10* have also been linked to both diseases. It is essential to do more research on patients suffering from Leśniewski-Crohn's disease and diabetes. The purpose of using GWAS is to estimate the frequency of single nucleotide

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polymorphisms in PTPN2 and PTPN22 [2]. Lu et al. proved that patients with CD or UC are more likely to suffer from T1D [3]. The common autoimmune background of diabetes and IBD, as well as the chronic inflammatory process, may cause the coexistence of these diseases.

Also, the effects of T1D in children and adolescents are compounded by inflammatory bowel disease. IBD leads to inefficient absorption of nutrients, which can cause frequent hypoglycemia, leading to chronic, imbalanced diabetes [4]. In long-term observation, nutrient malabsorption leads to malnutrition.

However, patients with IBD are often on other medications that affect glycemia. Glucocorticoids, 5-aminosalicylates, and thiopurines, tumor necrosis factor alpha (TNF-α) inhibitors, affect the metabolic control of diabetes. Studies have shown that aminosalicylates can affect a reduction of glycated hemoglobin (HbA1c) – which should be confirmed by more studies. Thiopurines seem to be a safe drug for use in patients with diabetes and IBD, provided that the state of the pancreas is monitored, but this needs to be confirmed by more studies. It is important to note that TNF-α inhibitors often cause a decrease in glycemia. That information is crucial in deciding the treatment method and insulin doses in patients with diabetes [5]. Long-term use of corticosteroids in UC may cause glucose intolerance in non-diabetic patients and, consequently, the development of type 2 diabetes (T2D) [6].

The intestinal microbiota contributes to maintaining the integrity of the intestinal barrier. It was observed that the bacteria producing butyrate in the fermentation process contribute to increasing the mucous layer. The mucous layer maintains the intestinal epithelium's integrity, supports T lymphocyte functioning, and reduces the risk of developing insulin resistance. Maintaining the integrity of the intestinal barrier reduces the incidence of diabetes and IBD. It follows that probiotic intestinal bacterial strains that produce butyrate may help treat and prevent diabetes and IBD. It is important that human phenotypes and human' intestinal microbiota phenotypes are very diverse. Species diversity may indicate the need to conduct molecular tests before administering a significant, therapeutic dose of probiotics because incorrect matching to the existing microbiota and the environment in the patient's intestines could be a negative health outcome of therapy [7].

Inflammatory bowel diseases and lipid disorders

Visceral adipose tissue is an active metabolic organ involved in lipid storage and immunological and hormonal activities. Inflammatory bowel disease infiltrates the surrounding adipose tissue along the mesentery. Mesenteric fat acts as a barrier against inflammation. At the same time, cytokines and adipokines responsible for inflammatory processes can originate from the mesenteric adipose tissue [8]. Intensification of the visceral tissue of the mesentery inflammation is caused by increased production of proinflammatory cytokines, which intensifies metabolic changes.

It has been shown that IBD is associated with changes in the composition and metabolism of gut microbiota (dysbiosis).

Gut microbiota is a primary regulator of the host's metabolism and has been shown to influence lipid levels in the blood and tissues. Lipids act as substrates for bacterial metabolic processes, and through their toxic effects, they inhibit some bacterial growth [9]. Studies on animal models have revealed diverse roles of gut biota, dependent on the health status, ranging from protective to proinflammatory actions. Furthermore, evidence from these experimental models suggests that although gut bacteria often drive immune activation, chronic inflammation alters the gut microbiota and contributes to dysbiosis [10].

Elevated levels of inflammatory cytokines may result in reduced activity of lipoprotein lipase (LPL), leading to a characteristic lipoprotein profile: increased levels of low-density lipoprotein cholesterol (LDL-c), total cholesterol (TC), triglycerides (TG), apolipoprotein B (ApoB), and decreased levels of high-density lipoprotein cholesterol (HDL-c). Disrupted lipid metabolism balance contributes to the acceleration of inflammatory reactions [11].

Gut microbiota influences lipid metabolism through the metabolites produced by gut flora, such as short-chain fatty acids (SCFA), secondary bile acids, and lipopolysaccharides - proinflammatory factors of bacterial origin [9]. Gut bacteria that ferment and produce SCFA are less abundant in the intestinal mucosa of patients with nonspecific inflammatory bowel disease compared to healthy individuals. SCFA are important metabolites in maintaining gut homeostasis and serve as fuel for intestinal epithelial cells, strengthening the gut barrier function. Recent discoveries also show

that short-chain fatty acids, especially butyrate, have immunomodulatory functions.

SCFA can also signal through surface receptors called G protein-coupled receptors (GPCRs) to activate signaling pathways that control immune processes.

Inflammatory bowel disease and cardiovascular diseases

CD and ulcerative colitis are associated with systemic inflammation and hypercoagulation. These factors may increase the risk of atherosclerosis and ischemic heart disease; therefore, in patients with IBD, a higher prevalence of cardiovascular diseases is observed. Proinflammatory markers, such as TNF-α, interleukin-6 (IL-6), and interleukin 1β (IL-1β), play an essential role in the pathogenesis of cardiovascular diseases and atherogenesis [12]. Researchers have reported an increase in TNF- α in patients with IBD and an increased level of proinflammatory interleukins [13,14]. The level of calprotectin (CLP), one of the acute phase proteins produced by neutrophils, has also been shown elevated in IBD. Clinically, calprotectin is considered to be an established prognostic marker of acute ischemic heart disease. Studies have shown that plasma calprotectin levels predict 12-month mortality in patients admitted with an ST-elevation myocardial infarction (STEMI) [15]. Moreover, recent studies have demonstrated an increased level of CRP in patients with IBD. These elevated levels of CRP have been associated with higher cardiovascular risk [16,17]. Accordingly, there are a significant number of cytokines and proteins connecting the occurrence of IBD with a higher risk of developing cardiovascular diseases.

There have been many studies showing an increased risk of developing ischemic heart disease in patients with IBD. In 2017, Feng et al. conducted a meta-analysis of 10 cohort studies, of which seven studies demonstrated a higher risk of cardiovascular disease in IBD patients. However, three of the included studies did not reveal such an association. Two cohort studies incorporated in the meta-analysis showed a decreased risk of acute myocardial infarction incidents among hospitalized patients diagnosed with IBD when compared with the general population. Moreover, the meta-analysis has indicated that the risk of Ischemic Heart Disease (IHD) was higher in women and younger patients (<50 years old) [18].

Similar results were obtained in a large cohort study of 29 090 220 patients presented in 2019 by Panhwar et al. This study demonstrated an increased risk of Myocardial Infarction (MI) in patients with IBD. It has been observed that the risk is highest in younger patients and diminishes with age. The increased risk of MI in younger patients may be explained by the fact that younger age at the time of IBD diagnosis is associated with its more aggressive course and acute inflammation. In comparison, the decline in risk with age among patients diagnosed later in life could be explained by the fact that the severity of the IBD tends to decrease over time. Data regarding gender differences revealed women with IBD (<45 years old) to be at higher risk of MI when compared to men with IBD. However, above 45 years of age, gender-related tendency disappears; thus, women and men with IBD show similar risk of MI. Moreover, the study demonstrated a higher prevalence of traditional cardiovascular risk factors (such as hypertension, smoking, obesity, and dyslipidemia) among patients with IBD in comparison to the general population. However, the increased risk of MI persisted even after adjusting for traditional cardiovascular risk factors, which indicate the presence of independent pathomechanisms connecting IBD with myocardial infarction [19].

At the same time, some studies reported a decreased risk of acute cardiac injury among patients with IBD compared to patients without the disease. It has been found that IBD did not link to increased in-hospital mortality as a consequence of MI. Nevertheless, patients diagnosed with IBD who have suffered MI were hospitalized for an extended period, and the total costs associated with their treatment were higher compared to patients without IBD [20]. Studies from recent years show an association between IBD and atherosclerosis. Chronic systemic inflammation may contribute to platelet aggregation and endothelial dysfunction, which are the factors of atherosclerosis and the development of cardiovascular diseases [21]. A review study and meta-analysis conducted by Hao Wu et al. demonstrated that IBD correlates with endothelial dysfunction and increased aortic stiffness. These factors play an essential role in the development of diseases correlated with atherosclerosis, such as coronary artery disease (CAD), peripheral artery disease (PAD), and stroke [22].

Patients with IBD have an almost 3-fold higher risk of developing venous thromboembolism in comparison

to the general population. The risk is significantly increased during periods of acute flares [23]. The study of Danish researchers, including 49799 IBD patients and 477504 patients from the control group, showed a significantly higher risk of venous thromboembolism (VTE), including deep venous thromboembolism (DVT) and pulmonary embolism (PE) in patients with IBD. Particularly high-risk groups included those under the age of 20. Abnormalities in coagulation and fibrinolysis could explain the increased risk in this group of patients. In the morphology of the IBD population, an elevated platelet number, aggregation, and decreased mean platelet volume have been observed [22].

Inflammatory bowel diseases and fatty liver

The exact relationship between IBD and Non-Alcoholic Fatty Disease (NAFLD) is not yet fully understood, but several factors may contribute to the development of NAFLD in people with IBD: Some medicines used to treat IBD, such as corticosteroids, may increase the risk of developing NAFLD. What is also highlighted here is the effect of the cancer necrosis factor on the development of NAFLD. Some studies have reported that the TNF-α inhibitor oxpentifillin may improve the prognosis of NAFLD in individuals with IBD [24].

IBD can interfere with the absorption and digestion of nutrients, leading to malnutrition. Malnutrition, especially protein, and vitamin deficiencies, may be an indication for parenteral treatment, and what is improperly and long used may contribute to the development of hepatic steatosis. This condition is prevalent in patients with active Crohn's disease, but decreased nutrition may also be observed in patients with active ulcerative colitis [25].

Intestinal endotoxemia also plays a vital role in the pathomechanism of hepatic steatosis in IBD patients: the lipopolysaccharide (bacterial endotoxin) binds to the lipopolysaccharide-binding protein (LBP), the resulting complex transports Cluster of Differentiation 14 (CD14) to the surface of KCs, which binds to toll-like receptor 4 (TLR4). Subsequently, the active Kupffer Cells (KCs) release TNF-α, IL-6, Reactive Oxygen Species (ROS), and Transforming Growth Factor Beta 1 (TGF-β1), resulting in insulin resistance, lipid peroxidation and HSC activation, which may eventually lead to NAFLD [26].

The diet used in IBD and metabolic diseases

A high-fiber diet reduces inflammation, which reduces the risk of atherosclerosis and coronary heart disease to which patients with IBD are exposed. It is recommended that the amount of fiber in the diet of patients with IBD be limited during exacerbations of the disease. However, during remission, this diet should not be associated with worsening patients' well-being [27].

Curcumin has an anti-inflammatory effect and may aid in the treatment of IBD. Curcumin inhibits myeloperoxidase and limits the production of interleukin-1 and neutrophil infiltration. Combining drug therapy with curcumin intake may reduce the risk of exacerbations of the disease and alleviate its symptoms, as well as reduce the risk of cardiovascular disease [28].

Consumption of dairy products in patients with IBD remains a controversial issue. Some studies say lactose-rich products can exacerbate IBD symptoms [29]. In contrast, recent studies have shown that dairy consumption is not associated with the recurrence of clinical signs in patients with IBD. The right amount of calcium promotes lowering blood pressure, increases the ratio of HDL to LDL, and reduces the risk of cardiovascular disease. In addition, it increases the sensitivity of cells to insulin, which prevents the development of insulin resistance, type 2 diabetes, and, consequently, metabolic syndrome [30].

Conclusions

1. There is a mutual dependency between diabetes and IBD.
2. IBD causes intestinal dysbiosis, which is essential in chronic inflammation and leads to insulin resistance, autoimmunity, and liver steatosis.
3. A proper diet reduces the severity of the inflammatory process in the intestine and the metabolic disorders associated with IBD.
4. IBD can lead to hypercoagulability, fibrinolysis, arterial stiffness, and endothelial dysfunction, which increases cardiovascular risk.

Conflict of interest
None

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