Review
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Nutrition and lifestyle factors associated with inflammatory bowel disease

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Abstract

Objective Many dietary and lifestyle factors are found to be associated with the pathogenesis of inflammatory bowel disease (IBD). The purpose of this study is to review the dietary and lifestyle factors associated with IBD. In addition too, this review attempts to investigate the association between dietary patterns and IBD risk and compare lifestyle factors among IBD patients.

Methods Google Scholar and PubMed were searched together with relevant journals for English studies from September 2018 to August 2020. The original studies which evaluated the lifestyle factors and dietary patterns as risk factors for inflammatory bowel disease were included.

Results Several studies in IBD were discussed, and highlighted the independent effects of various dietary and lifestyle factors on the risk of IBD. Forty-nine (49) articles met the inclusion criteria and indicated that dietary factors tend to play a pivotal role in the disease etiopathogenesis and course. However, research on food and IBD is contradictory.

Conclusions An excessive intake of sugar and animal fat is considered a risk factor for the development of IBD, whereas a high fiber diet and high intake of fruits and vegetables may play a protective effect. The role of lifestyle factors in IBD is crucial. Amply of evidence suggested that smoking is a causative agent in Crohn's disease while it is protective against ulcerative colitis. Stress, depression, vitamin D deficiency, and impaired sleep have all been all associated with incident IBD. A diet with a modified carbohydrate composition, a semi-vegetarian diet, a diet low in protein and fat, and a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols should be taken into consideration for IBD patients.

Keywords Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Lifestyle factors; Nutrition.

Introduction:

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of unknown etiology that is thought to result from a complex interaction of genetic predisposition (leading to immunological abnormalities), dysbiosis of the gut microbiota, and environmental influences. However, none of the risk factors alone were sufficient for disease development, but the complex interactions between each factor play a major role leading to the development of IBD.[1] These risk factors alone or in combination may play a significant role in the development of IBD.[2] The incidence of IBD has been increasing in both developing and developed nations and this is hypothesized to be in part related to the change in dietary and lifestyle factors associated with modernization.[3] Huang et al. (2016) found that abnormal innate immune responses may induce adaptive immunity imbalance, where inflammatory cytokines produced may increase innate immune damages, abate intestinal barrier functions, and aggravate inflammation.[4] Additionally, an immunological imbalance of the intestinal mucosa, mainly associated with cells of the adaptive immune system, which responds against self-antigens, produces chronic inflammatory conditions in these patients, and it is thought that aberrant and continuing immune response to the microbes in the gut, catalyzed by genetic susceptibility of the individual, maintains ongoing intestinal mucosal inflammation.[5] Subsequently, this ongoing inflammation damages the intestinal wall, leading to diarrhea, bleeding and abdominal pain.[6] Fig. 1 shows the complex pathogenesis of IBDs.[3]

IBD has an increasing incidence and prevalence in most countries and becomes a global emerging disease.[3] A westernized lifestyle, personal habits, and environmental factors have been found to contribute to the pathogenesis of IBD.[7] The relevant risk factors (including smoking, hygiene hypothesis, microorganisms, appendectomy, medication, nutrition, and stress) have all been associated with the pathogenesis of IBD.[8] However, the exact specific mechanism underlying the association between environmental factors and IBD is still poorly understood.[6] The treatment of IBD in any given patient may have several different goals, such as relief of symptoms: abdominal pain, rectal bleeding, and diarrhea; induction of remission in patients with active disease; prevention of relapse; correction of nutritional deficiencies; healing of fistulas; and avoidance of emergency surgery with the ultimate goal of improving quality of life.[9] The current drug therapy including the use of anti-inflammatory agents and immunomodulators and biologic agents may reduce the symptoms associated with IBD and achieve long-term remission, and also therapy may be modified to some extent based on the severity, disease location, extraintestinal manifestations, and associated complications.[10]

Materials and methods

A critical review was performed by defining a scope review and collect relevant data sources and review literature, the application of literature to the current study.[11] Electronic databases such as PubMed, Google Scholar, and relevant Journals

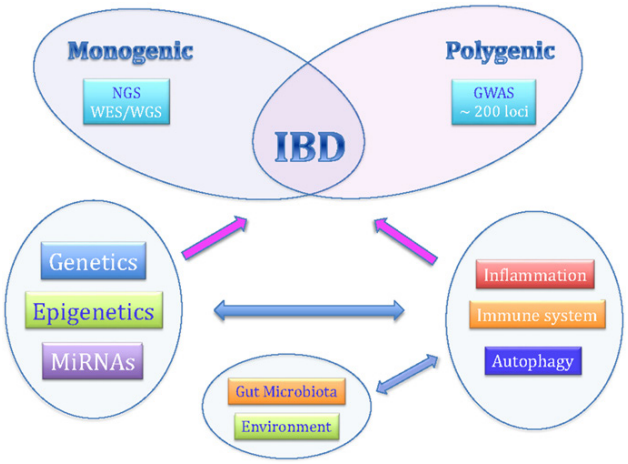

Fig. 1 **The complex pathogenesis of inflammatory bowel diseases (IBD).[3]**
Abbreviations: NGS (Next Generation Sequencing), WGS (Whole Genome Sequencing), WES (Whole Exome Sequencing), GWAS (Genome-Wide Association Studies) and MiRNAs (Micro Ribonucleic Acids).

were systematically searched for English language publications from September 2018 to August 2020. The inclusion criteria were: (1) Studies concerning IBD (including Crohn's disease (CD) and ulcerative colitis) diagnosed using any well-established criteria. (2) Studies examining quality of life. (3) Studies with adult populations; controlled studies, including randomized controlled trials (baseline data only), with prospective, retrospective, or cross-sectional designs. (4) Peer-reviewed papers. (5) Studies focusing on other psychological variables such as depression, anxiety, distress, coping, or personality, and lifestyle factors like smoking and physical activity. Articles with interventional studies (e.g., medication trials); studies in languages other than English; conference abstracts or any short papers with incomplete data presented; case reports, case series, or qualitative research and animal studies were excluded.

Titles and abstracts were screened by two authors (TQ and RT) for possible inclusion in the study following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] Appropriate studies were assessed with regards to the inclusion and exclusion criteria. Full texts of selected studies were carefully shortlisted regarding the eligibility criteria and methodological aspects. Original articles investigated the lifestyle factors and dietary patterns as risk factors for IBD were included. After reviewing the full texts, all authors were involved in analysis and reaching consensus on the factors emerging from the data. The data extraction included authors, year of publication, country of origin, design, setting, participant characteristics (IBD subtype, age, sex, disease activity status) and sample size, outcome measures, and results for main outcome measures.

Results

Of the 786 studies identified during the database searches, 205 were removed as duplicates. Titles and abstracts were screened for the remaining 581 papers, and 346 did not meet the inclusion criteria, leaving 217 included for full review. A total of 49 unique studies were included in the final review by reading a full text. Fig. 2 shows the paper selection process based on PRISMA 2009 flowchart.[12]

Inflammatory bowel disease and body mass index

The relationship between body mass index (BMI) and problems associated with IBD, such as morbidity, complications, prognosis, the stage of the disease, and medical therapy, have been found in many studies. One study revealed that in IBD patients, BMI was lower than that in non-IBD controls.[13] Another study indicated that ulcerative colitis (UC) patients have higher BMI than controls or have a BMI in the normal range.[14] Other studies showed that BMI was decreased in patients with active UC, but not in patients with CD, compared with healthy controls.[15]

On the contrary, others found that patients with inactive CD had a lower body weight and BMI value when compared with both UC and healthy controls.[16] Few studies have shown that medical therapy may decrease lean mass.[17,18] Another study indicated that patients' BMI is lower than controls before the use of therapy.[19] Dong et al. (2015) found that medical therapy, including corticosteroid, azathioprine, mesalamine, and TNF-alpha antagonists, may improve BMI in patients with CD. However, the authors found that without therapy, Crohn's patients' BMI was significantly lower than non-IBD controls, while with medical treatment, the difference was not statistically significant.[14]

Obesity may contribute to IBD development through several mechanisms. IBD was found to be associated with excess adipocyte hypertrophy generating a pro-inflammatory state through secretion of inflammatory cytokines and chemokines, including interleukin (IL)-1β, IL-6, IL-8, monocyte chemoattractant factor (MCP-1), tumor necrosis factor-α (TNF- α), and C-reactive protein; CRP.[15] These biofactors are closely related to the pathogenesis of IBD.[15] Epidemiological studies have shown a parallel rise in the prevalence of obesity and immune-mediated conditions, including IBD. This association may produce a host pro-inflammatory response that originates from adipokines produced by visceral and subcutaneous fat.[15,20] Reduced level of adiponectin plays a permissive role in the release of pro-inflammatory cytokines (TNFα; CRP; interleukin-6: IL-6; vascular cell adhesion molecule-1: VCAM 1; and MCP-1), additionally, insulin resistance is promoted by the interaction of TNFα and insulin receptor through a decrease in tyrosine kinase, and this promotes oxidative stress which can impact intestinal bacteria.[21] Moreover, alterations in the intestinal microbiome contribute to dysbiosis as well as to altered intestinal permeability which then, in turn, contributes to promoting the pro-inflammatory state like IBDs.[20] Fig. 3 shows the effect of obesity on the development of IBD.[20]

Mendall et al. (2011) documented that there was a significant association between obesity at diagnosis for CD but not with UC in their case–control study for IBD patients attending gastroenterology clinics. Their study aimed to determine whether obesity at diagnosis is a risk factor for CD and UC versus community controls and whether there is a U-shaped relationship between BMI at diagnosis and risk of CD versus UC. The authors revealed that obesity at diagnosis was more common in subjects with CD versus UC with an odds ratio of 2.02 (1.18–3.43) p = 0.0096 and also CD versus community controls in the 50–70 year age group (odds ratio 3.22 (1.59–6.52) p=0.001).[22] There was evidence of a 'dose–response'

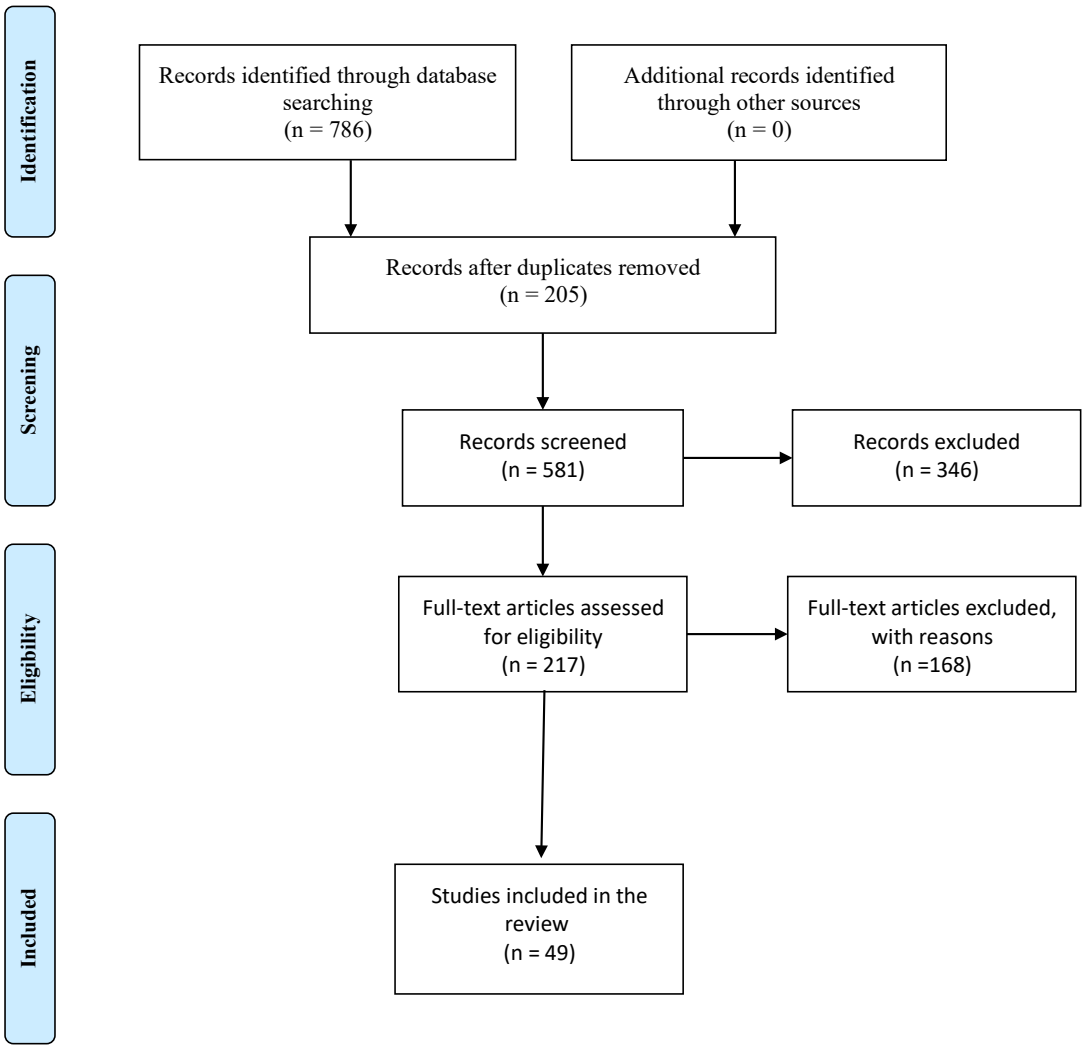

Fig. 2 **The paper selection process based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA 2009 flowchart.[12]**

phenomenon with increasing degrees of obesity-associated with increased disease risk. Low BMI at diagnosis was also associated with the risk of CD versus UC. A U-shaped relationship between BMI and risk of Crohn's was supported by the strong inverse association of BMI at diagnosis (p=0.0001) and positive association of BMI at diagnosis squared (p = 0.0002).[22] However, another hypothesis of the relationship between obesity and IBD was reported by Chan et al. (2013), they found out that there was no association with the four higher categories of BMI compared with a normal BMI for UC (P *trend*=0.36) or CD (P *trend*=0.83). The lack of association was consistent when BMI was analyzed as a continuous or binary variable (BMI 18.5<25.0 vs. ≥ 25 kg/m^2), they concluded that obesity, as measured by BMI, is not associated with the development of incident UC or CD.[23]

Inflammatory bowel disease and malnutrition

Nutrition plays a pivotal role in the clinical care of patients with IBD. In broad terms, nutritional therapy can be considered as supportive or even a primary treatment. Supportive therapy aims to correct malnutrition and micronutrient deficiencies and reverse their metabolic pathological consequences, in addition to providing advice on specific dietary regimes.[24] Patients with IBD often suffer from nutritional deficiencies. Malnutrition is characterized by weight loss, growth failure, and micronutrient depletion.[24] A study by Nguyen et al. (2008) examined the prevalence of clinically diagnosable malnutrition among hospitalized patients with IBD in the United States and whether this malnutrition influenced health outcomes. The authors revealed that the prevalence of malnutrition was greater in CD and UC patients than in non-IBD patients (6.1% and 7.2% *vs* 1.8%, p<0.0001). The adjusted odds ratio for malnutrition among IBD admissions compared with non-IBD admissions was 5.57 [95% CI: 5.29–5.86]. Additionally, there was an increased likelihood of malnutrition among those with fistulizing CD (OR 1.65; 95% CI: 1.50–1.82) and those who had undergone bowel resection (OR 1.37; 95% CI: 1.27–1.48). Malnutrition was associated with increased in-hospital mortality (OR 3.49; 95% CI: 2.89–4.23). This study suggests that malnutrition may serve as a clinical marker of poor IBD prognosis in hospitalized patients.[25]

Inflammatory bowel disease and physical activity

Physical activity may play a role in reducing the risk of diverticulosis, gastrointestinal hemorrhage, and inflammatory

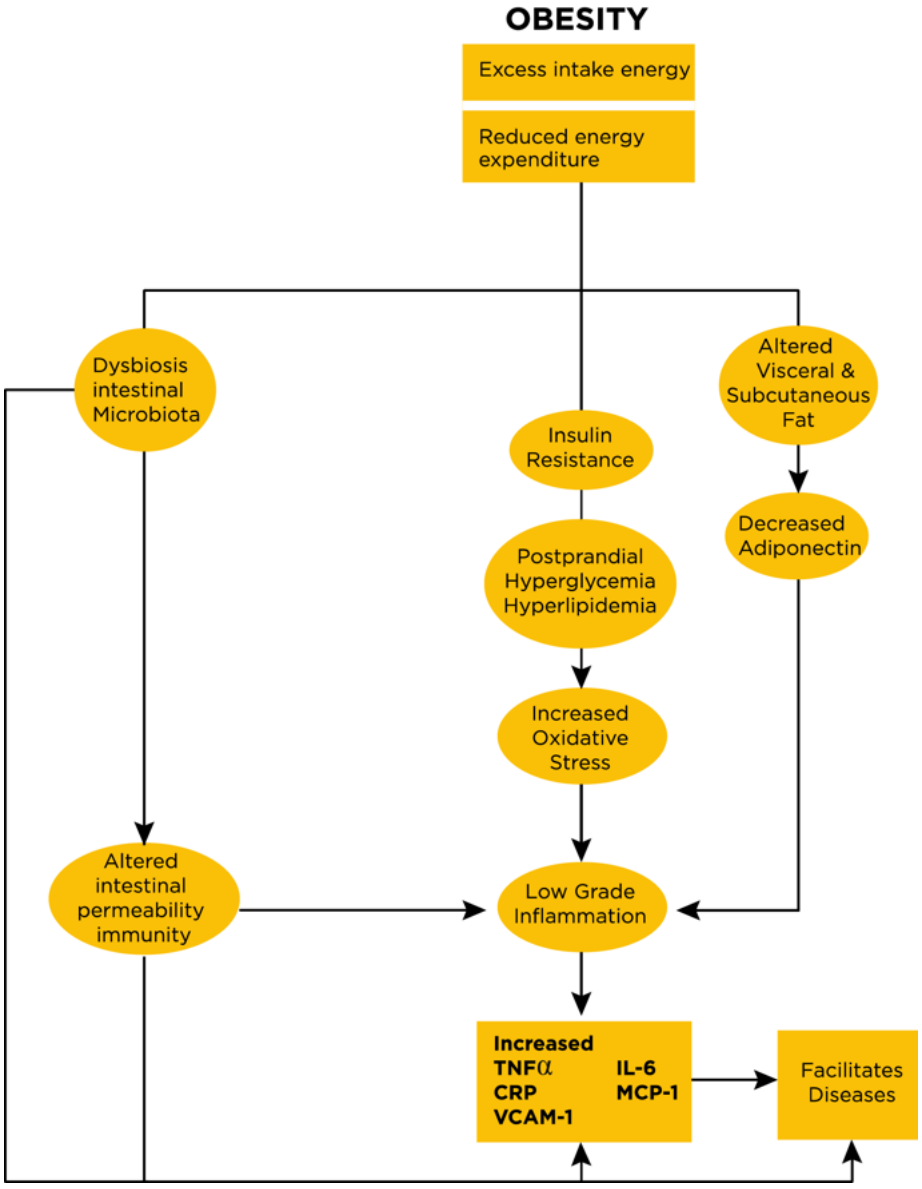

Fig. 3 **The effect of obesity on developing Inflammatory Bowel Disease (IBD).**[20]
Abbreviations: TNFα (Tumor Necrosis Factor-alpha), CRP (C - reactive protein), VACAM-1 (Vascular Cell Adhesion Molecule-1), IL-6 (Interleukin-6) and MCP-1 (Monocyte Chemoattractant Protein-1).

bowel disease.[26] Current research revealed that exercise may be beneficial to reduce stress and symptoms of IBD, and also recommends exercise to help counteract some IBD specific complications by improving bone mineral density, immunological response, psychological health, weight loss, and stress management ability.[27]

A host of environmental factors may contribute to the onset of IBD. Several studies examined the role of physical activity and active lifestyle as potential protective factors in the development of IBD. Ng et al. (2015) found a protective effect of exercise and onset of CD (OR: 0.58; 95% CI: 0.4–1.0), but none for UC, when comparing 186 CD patients, 256 UC patients and 940 controls matched for age, sex, and geographical location.[28] A case–control study in a Slovakian population found a statistically significant association between lower weekly rates of sport participation among adolescent and the development of IBDs (OR: 2.7, 95% CI: 1.5–5.0).[29] However, Chan et al. (2013) found in a prospective cohort study of 177 UC and 75 CD patients that there was no association between physical activity levels and UC, (P-trend=0.79) or CD (P-trend=0.42) [23].

Inflammatory bowel disease and lifestyle factors

The role of lifestyle factors in IBD is crucial. Smoking was first established as a risk factor in the development of IBD more than 30 years ago.[30] Smoking is one of the most important and well-characterized environmental risk factors for IBD, but its pathogenic mechanism is not clear. Evidence from studies suggested that smoking is a causative agent in CD while it is protective against UC.[31,32] The association between smoking and UC was first described by Harries et al. (1982) who noted a reduced frequency of smokers among patients with UC compared to healthy controls.[30] The effect of smoking on the localization and clinical course of 231 patients with CD was studied by Lindberg et al. (1992) who found that heavy smokers (greater than 10 cigarettes/d) had small bowel CD more

often than patients that smoked (less than 10 cigarettes/d) (p = 0.045).[33] Van der Heide et al. (2009) found that no detrimental effects of active smoking on CD were observed, but passive smokers had higher need of immunosuppressant and infliximab-based therapy more frequently than non-passive smokers. Additionally, the authors found that active smoking had beneficial effects on UC, indicated by reduced rates of colectomy, primary sclerosing cholangitis, and backwash-ileitis in active smokers compared to never smokers.[34] Furthermore, Cosnes et al. (1999) found that early smoking significantly increases the risk of CD [OR 2.0 (1.65–2.47)], also CD patients who smoke had a worse course of illness and quality of life, and were more likely to develop complications. Additionally, they had a higher rate of hospitalizations, showed a worse response to treatments, and had a greater need for surgery.[35]

The mechanisms of the effect of smoking in IBD are complex, involving different chemicals found in the cigarette, such as nicotine, free radicals, and carbon monoxide, that can act on different targets, including mucus layer, cytokine production, macrophage function, and microvasculature.[36]

Both smoking and nicotine affect the cytokine profile, predominantly by reducing the production of proinflammatory cytokines. Smokers with active inflammatory bowel disease have significantly lower concentrations of IL-1β and IL-8 in patients with UC, and IL-8 in patients with CD than in non-smokers.[37] Other evidence suggested that in patients with CD, when a high concentration of cigarette particulate matter reaches the ileum, it may alter the interaction of the intestinal mucosa with the microbiota through several mechanisms, e.g., affecting bacterial clearance, changing microbiota composition, increasing the permeability of the intestinal barrier, and dysregulating immune responses.[32] On the contrary, people who have UC have a thinner mucus layer in the left colon and rectum when compared to healthy people. Thus, it has been proposed that nicotine may increase the production of mucus and suppress the immune system which subsequently prevents inflammation in the colon.[37] Another theory states that nitric oxide, released by nicotine, may reduce muscle activity in the colon.[39]

Many other lifestyle factors are likely to enhance the risk of developing IBD. Stress reduces mucus secretion and increases intestinal permeability of colon in a mouse model.[40] Bitton et al. (2008) documented the association between major life stress factors, anxiety, depression, and IBD risk. The authors showed that participants with higher stress suffered from more relapses of both UC and CD. Also, the presence of anxiety or depression has been associated with increased disease activity and an increased risk of surgery in CD patients.[41]

Inflammatory bowel disease and dietary patterns

Diet was suspected to be an environmental factor involved in the etiology of IBD.[42] Experimental models showed that diet contributed to gut inflammation through several mechanisms including antigen presentation, alteration of gut permeability, and changes in the composition of the gut microbiota.[42-44]

The Mediterranean diet has long been accepted as an example of a well-balanced diet but a gold-standard "Mediterranean diet" is lacking.[45] At least 16 countries border the Mediterranean Sea, variation in Mediterranean diet among these countries as well as among regions within the same country is well known.[46] However, despite the above variation, a Mediterranean diet has the following common characteristics: high consumption of fruits, vegetables, bread, other cereals, potatoes, beans, nuts, and seeds; low to moderate consumption of dairy products, fish, eggs, and poultry; and infrequent consumption of red meat.[47] In the Mediterranean diet, olive oil is frequently consumed which is an important monounsaturated fat source and wine is consumed in low to moderate amounts as well.[48] The combination and range of foods included in this dietary pattern provide plenty of antioxidants such as flavonoids, carotenoids, and antioxidant vitamins, lots of phytochemicals including phytoestrogens, sufficient quantities of fiber, adequate folate, and a favorable fatty acid profile.[45] A growing body of scientific evidence indicated that the Mediterranean dietary pattern was associated with significant improvements in health status and a decrease in inflammatory markers.[47,49]

The protective effect of the Mediterranean diet was hypothesized to be derived from the balance in the omega-6/omega-3 ratio of the Mediterranean diet pattern (35% total fat: 15% monounsaturated fatty acids (MUFA) (mainly from olive oil), 13% saturated fatty acids (SFA), and 6% polyunsaturated fatty acids (PUFA).[50] Additionally, adherence to the Mediterranean diet pattern has been shown to beneficially affect the gut microbiome and gut metabolites (metabolome).[51] Also, there was a large body of evidence showing that Mediterranean dietary patterns regulate inflammation in chronic disease.[51,52] A case–control study (n = 264 IBD subjects and 203 controls) found that low adherence to the Mediterranean dietary pattern was a significant risk factor in the development of pediatric UC (OR: 2.3; CI: 12–4.5).[51]

In addition, other dietary patterns were found to be associated with the risk of IBD, such as Western dietary pattern which is high in meat, dairy products, fat, sugary foods, processed meats, pastries, baked goods, confectionery, sweetened drinks, alcohol, and limited amounts of vegetables and fruits.[9] IBD has traditionally been thought of as a disease of the Western hemisphere, however, there is an increased incidence in Japan, Hong Kong, Korea, and Eastern Europe, although still not as common, an increasing incidence of IBD is identified in South Africa, South America, and Saudi Arabia as well.[53] The dramatic rise in the incidence of IBD, particularly in South Asia, India, and Japan, traditionally low incidence countries, suggested that environmental factors, such as Western dietary pattern, may play an important role in disease pathogenesis.[28] Migration from a low incidence country to a high incidence country increases the risk of developing IBD.[54] A Western diet that contains pro-inflammatory food cytokines, can modulate intestinal permeability, and alter the intestinal microbiota promoting a low-grade chronic inflammation in the gut which is considered an important risk factor and a prerequisite in the development of UC.[54] A case–control study conducted in Iran on newly diagnosed UC patients (n = 62 UC patients, 124 controls) showed that subjects that had a higher dietary inflammatory index (pro-inflammatory diet) had an increased risk of developing UC (OR: 1.55, 95% CI: 1.04–2.32.[55] Shivappa et al. (2016) concluded that encouraging intake of more anti-inflammatory dietary factors, such as plant-based foods rich in fiber and phytochemicals, and reducing intake of pro-inflammatory factors, such as fried or processed foods rich in transfatty acids, could be a potential strategy for reducing the risk of UC.[55] A meta-analysis showed an inverse association between the intake of vegetables and fruit and CD, with a pooled OR for the highest versus lowest

consumption of fruit = 0.57(95% CI 0.44–0.74).[56] However, patients who consumed a pro-inflammatory diet (e.g., high in animal protein, low in fruit and vegetables) have demonstrated a higher risk of ulcerative colitis.[56]

A prospective trial conducted in Japan in hospitalized subjects with CD (n=22) examined the effect of a semi-vegetarian diet on maintaining remission. The diet was Lacto-Ovo vegetarian, in which eggs and milk were allowed with small portions, meat offered once every 2 weeks and fish weekly. The remission rate, a period which symptoms of disease were reduced or disappeared, achieved with the semi-vegetarian diet was 100% after 1 year and 92% after 2 years. A semi-vegetarian diet showed significant prevention of relapse ($p = 0.003$ log-rank test). Based on these observations, the semi-vegetarian diet may be a highly effective way to maintain a remission CD.[57] Furthermore, the rise in the incidence of IBD in countries that had a very low incidence suggested that industrialization and adoption of the westernized diet may be a risk factor in the development of IBD, additionally reduced consumption of fruits and possibly vegetables, resulting in a reduced overall intake of fiber, with higher intake of meats, fast foods, and transfatty acids appeared to be associated with an overall increase in the risk of developing IBD.[58]

A case–control study carried out by Sakamoto et al. (2005) revealed that a higher consumption of sweets was positively associated with UC risk [OR for the highest *vs* lowest quartile, 2.86; 95% CI, 1.24–6.57], whereas the consumption of sugars and sweeteners (OR, 2.12; 95% CI, 1.08–4.17), sweets (OR, 2.83; 95% CI, 1.38–5.83), fats and oils (OR, 2.64; 95% CI, 1.29–5.39), and fish and shellfish (OR, 2.41; 95% CI, 1.18–4.89) were positively associated with CD risk. For nutrients, the intake of vitamin C (OR, 0.45; 95% CI, 0.21–0.99) was negatively related to UC risk, while the intake of total fat (OR, 2.86; 95% CI, 1.39–5.90), MUFAs (OR, 2.49; 95% CI, 1.23–5.03) and polyunsaturated fatty acids (OR, 2.31; 95% CI, 1.12–4.79), vitamin E (OR, 3.23; 95% CI, 1.45–7.17), and n-3 fatty acids (OR, 3.24; 95% CI, 1.52–6.88) and n-6 fatty acids (OR, 2.57; 95% CI, 1.24–5.32) were positively associated with CD risk.[59] Geerling et al. (2000) found that high intakes of monounsaturated fat (OR: 33.9 [95% CI 2.6–443.1]), polyunsaturated fat (OR: 5.1 [95% CI 1.0–26.7]), and vitamin B6 (OR: 6.9 [95% CI 1.6–30.7] were associated with an increased risk to develop UC.[60] In a case–control study conducted in Jordan by Rayyan et al. (2021), the authors showed that IBD patients showed significant increase in the intake of saturated fat, protein, carbohydrates, sugars, fiber, MUFA, trans-fat cholesterol, vitamins A, D, E, B12, C and folate, beta-carotene, retinol, calcium, potassium, iron, Omega-3 and Omega-6 compared to the control group. However, the control group showed higher intake of vitamin K and caffeine when compared to the IBD patients ($p < 0.05$).[61]

Conclusion

In this review, we found that IBD is chronic relapsing intestinal inflammatory disease characterized by complex interactions of multiple factors including smoking, major life stressors, diet, and lifestyle. Various dietary and nutritional factors have been suggested as being significant etiological factors both for CD and UC. However, research on food and IBD is contradictory. An excessive intake of sugar and animal fat is considered a risk factor for the development of IBD, whereas a high fiber diet and high intake of fruits and vegetables may play a protective effect. The role of lifestyle factors in IBD is crucial. Amply of evidence suggested that smoking is a causative agent in CD while it is protective against UC. Stress, depression, vitamin D deficiency, and impaired sleep have all been all associated with incident IBD. A diet with a modified carbohydrate composition, a semi-vegetarian diet, a diet low in protein and fat, and a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols should be taken into consideration for IBD patients.

Competing interests

The authors declare that they have no competing interest.

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References

1. Molodecky, NA, Kaplan, GG (2010), Environmental risk factors for inflammatory bowel disease. Gastroenterol Hepatol 2010;6(5), 339.
2. Frolkis, A, Dieleman, LA, Barkema, HW, Panaccione, R, Ghosh, S, Fedorak, RN, Alberta IBD Consortium, Environment and the inflammatory bowel diseases. Can J Gastroenterol, 2013:27.
3. Loddo, I, Romano, C, Inflammatory bowel disease: genetics, epigenetics, and pathogenesis. Front Immunol 2015;6:551.
4. Huang, Y, Chen, Z, Inflammatory bowel disease related innate immunity and adaptive immunity. Am J Transl Res 2016;8(6):2490.
5. Bonen, DK, Cho, JH, The genetics of inflammatory bowel disease. Gastroenterology, 2003;124(2):521-536.
6. O'Sullivan, M, O'Morain, C, Nutrition in inflammatory bowel disease. Best Pract Res Clin Gastroenterol, 2006;20(3):561-573.
7. Manzel, A, Muller, DN, Hafler, DA, Erdman, SE, Linker, RA, Kleinewietfeld, M. Role of "Western diet" in inflammatory autoimmune diseases. Curr Allergy Asthma Rep, 2014;14(1):404.
8. Ye, Y, Pang, Z, Chen, W, Ju, S, Zhou, C. The epidemiology and risk factors of inflammatory bowel disease. Int J Clin Exp Med 2015;8(12), 22529.
9. Pithadia, AB, Jain, S., Treatment of inflammatory bowel disease (IBD). Pharmacol Rep, 2011;63(3), 629-642.
10. Rutgeerts, P, Van Assche, G, Vermeire, S. Optimizing anti-TNF treatment in inflammatory bowel disease. Gastroenterology, 2004;126(6):1593-1610.
11. Carnwell, R, Daly, W. Strategies for the construction of a critical review of the literature. Nurse Educ Pract,2001;1(2):57-63.
12. Moher, D, Liberati, A, Tetzlaff, J, Altman, DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med,2009;6(7):e1000097.
13. Ghosha C, Shukla, A. Malnutrition in inflammatory bowel disease patients in northern India: frequency and factors influencing its development. 2008.
14. Dong, J, Chen, Y, Tang, Y, Xu, F, Yu, C, Li, Y, Dai, N. Body mass index is associated with inflammatory bowel disease: a systematic review and meta-analysis. PLoS One, 2015;10(12):e0144872.
15. Flores, A, Burstein, E, Cipher, DJ, Feagins, LA. Obesity in inflammatory bowel disease: a marker of less severe disease. Digest Dis Sci, 2015;60(8):2436-2445.
16. Capristo, E, Mingrone, G, Addolorato, G, Greco, AV, Gasbarrini, G. Metabolic features of inflammatory bowel disease in a remission phase of the disease activity. J Intern Med, 1998;243(5):339-347.
17. Geerling, BJ, Badart-Smook, A, Stockbrügger, RW, Brummer, RJ. Comprehensive nutritional status in patients with long-standing Crohn disease currently in remission. Am J Clin Nutr, 1998;67(5):919-926.
18. Mijač, DD, Janković, GL, Jorga, J, Krstić, MN. Nutritional status in patients with active inflammatory bowel disease: prevalence of malnutrition and methods for routine nutritional assessment. Eur J Intern Med, 2010;21(4):315-319.

19. Cravo, M, Guerreiro, CS, dos Santos, PM, Brito, M, Ferreira, P, Fidalgo, C, Pereira, AD. Risk factors for metabolic bone disease in Crohn's disease patients. Inflam Bowel Dis, 2010;16(12):2117-2124.
20. Szilagyi, A. Relationship (s) between obesity and inflammatory bowel diseases: possible intertwined pathogenic mechanisms. Clin J Gastroenterol, 2019;1-14.
21. Balistreri, CR, Caruso, C, Candore, G. The role of adipose tissue and adipokines in obesity-related inflammatory diseases. Mediat Inflam, 2010.
22. Mendall, MA, Gunasekera, AV, John, BJ, Kumar, D. Is obesity a risk factor for Crohn's disease? Digest Dis Sci, 2010;56(3):837-844.
23. Chan, SS, Luben, R, Olsen, A, Tjonneland, A, Kaaks, R, Teucher, B, Bergmann, MM. Body mass index and the risk for Crohn's disease and ulcerative colitis: data From a European Prospective Cohort Study (TheIBDin EPIC Study). Am J Gastroenterol, 2010;108(4):575-582.
24. Goh, J, O'morain, CA. Nutrition and adult inflammatory bowel disease. Aliment Pharmacol Therap, 2003;17(3):307-320.
25. Nguyen, GC, Munsell, M, Harris, ML. Nationwide prevalence and prognostic significance of clinically diagnosable protein-calorie malnutrition in hospitalized inflammatory bowel disease patients. Inflam Bowel Dis, 2008;14(8):1105-1111.
26. Strate, LL, Liu, YL, Aldoori, WH, Giovannucci, EL. Physical activity decreases diverticular complications. Am J Gastroenterol, 2009;104(5):1221.
27. Narula, N, Fedorak, RN. Exercise and inflammatory bowel disease. Can J Gastroenterol Hepatol, 2008;22(5):497-504.
28. Ng, SC, Tang, W, Leong, RW, Chen, M, Ko, Y, Studd, C, Kasturiratne, A. Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific. Gut, 2015;64(7):1063-1071.
29. Hlavaty, T, Toth, J, Koller, T, Krajcovicova, A, Oravcova, S, Zelinkova, Z, Huorka, M. Smoking, breastfeeding, physical inactivity, contact with animals, and size of the family influence the risk of inflammatory bowel disease: A Slovak case–control study. United Eur Gastroenterol J, 2013;1(2):109-119.
30. Harries, AD, Baird, A, Rhodes, J. Non-smoking: a feature of ulcerative colitis. Br Med J, 1982;284(6317):706.
31. Legaki, E, Gazouli, M. Influence of environmental factors in the development of inflammatory bowel diseases. World J Gastroint Pharmacol Therap, 2016;7(1):112.
32. Qalqili T, Rayyan Y, Tayyem R. Nutrition and Lifestyle Factors Associated with Inflammatory Bowel Disease. J Gastroint Liver Dis JGLD, 2021;30(1), In Press.
33. Lindberg, E, Järnerot, G, Huitfeldt, B. Smoking in Crohn's disease: effect on localisation and clinical course. Gut,1992; 33(6):779-782.
34. Van der Heide, F, Dijkstra, A, Weersma, RK, Albersnagel, FA, van der Logt, EM, Faber, KN, Dijkstra, G. Effects of active and passive smoking on disease course of Crohn's disease and ulcerative colitis. Inflam Bowel Dis, 2009;15(8):1199-1207.
35. Cosnes, J, Carbonnel, F, Carrat, F, Beaugerie, L, Cattan, S, Gendre, J. Effects of current and former cigarette smoking on the clinical course of Crohn's disease. Aliment Pharmacol Therap, 1999;13(11):1403-1411.
36. Loftus Jr, EV. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology, 2004;126(6):1504-1517.
37. Bhatti, MA, Hodgson, HJF. Peripheral blood pro-inflammatory cytokine profile in active inflammatory bowel disease (IBD) differ between smokers and non-smokers. Gut, 1997;40(3S).
38. Salih, A, Widbom, L, Hultdin, J, Karling, P. Smoking is associated with risk for developing inflammatory bowel disease including late onset ulcerative colitis: a prospective study. Scand J Gastroenterol, 2018;53(2):173-178.
39. Mahid, SS, Minor, KS, Soto, RE, Hornung, CA, Galandiuk, S. Smoking and inflammatory bowel disease: a meta-analysis. In Mayo Clinic Proceedings (Vol. 81, No. 11, pp. 1462-1471). Elsevier. 2006.
40. Cosnes, J. Smoking, physical activity, nutrition and lifestyle: environmental factors and their impact on IBD. Digest Dis, 2010;28(3):411-417.
41. Bitton, A, Dobkin, PL, Edwardes, MD, Sewitch, MJ, Meddings, JB, Rawal, S, Wild, GE. Predicting relapse in Crohn's disease: a biopsychosocial model. Gut, 2008;57(10):1386-1392.
42. Racine, A, Carbonnel, F, Chan, SS, Hart, AR, Bueno-de-Mesquita, HB, Oldenburg, B, Key, T. Dietary patterns and risk of inflammatory bowel disease in Europe: results from the EPIC study. Inflam Bowel Dis, 2016;22(2):345-354.
43. Chapman-Kiddell, CA, Davies, PS, Gillen, L, Radford-Smith, GL, Role of diet in the development of inflammatory bowel disease. Inflam Bowel Dis, 2010;16(1):137-151.
44. Nickerson, KP, McDonald, C. Crohn's disease-associated adherent-invasive Escherichia coli adhesion is enhanced by exposure to the ubiquitous dietary polysaccharide maltodextrin. PLoS One, 2012;7(12):e52132.
45. Demetriou, CA, Hadjisavvas, A, Loizidou, MA, Loucaides, G, Neophytou, I, Sieri, S, Kyriacou, K. The mediterranean dietary pattern and breast cancer risk in Greek-Cypriot women: a case-control study. BMC Cancer, 2012;12(1):113.
46. Karimi, Z, Jessri, M, Houshiar-Rad, A, Mirzaei, HR, Rashidkhani, B. Dietary patterns and breast cancer risk among women. Public Health Nutr, 20141;7(5):1098-1106.
47. Estruch, R. Anti-inflammatory effects of the Mediterranean diet: the experience of the PREDIMED study. Proc Nutr Soc, 2010;69(3):333-340.
48. Castello, A, Pollán, M, Buijsse, B, Ruiz, A, Casas, AM, Baena-Cañada, JM, Lluch, A. Spanish Mediterranean diet and other dietary patterns and breast cancer risk: case–control EpiGEICAM study. Br J Cancer, 2014;111(7):1454-1462.
49. Altomare, R, Cacciabaudo, F, Damiano, G, Palumbo, VD, Gioviale, MC, Bellavia, M, Monte, AIL. The mediterranean diet: a history of health. Iran J Public Health, 201342(5):449.
50. De Filippis, F, Pellegrini, N, Vannini, L, Jeffery, IB, La Storia, A, Laghi, L, Turroni, S. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. Gut, 2016;65(11):1812-1821.
51. Strisciuglio, C, Giugliano, F, Martinelli, M, Cenni, S, Greco, L, Staiano, A, Miele, E. Impact of environmental and familial factors in a cohort of pediatric patients with inflammatory bowel disease. J Pediat Gastroenterol Nutr, 2017;64(4):569-574.
52. Marlow, G, Ellett, S, Ferguson, IR, Zhu, S, Karunasinghe, N, Jesuthasan, AC, Ferguson, LR. Transcriptomics to study the effect of a Mediterranean-inspired diet on inflammation in Crohn's disease patients. Human Genomics, 2013;7(1):24.
53. Lovasz, BD, Golovics, PA, Vegh, Z, Lakatos, PL. New trends in inflammatory bowel disease epidemiology and disease course in Eastern Europe. Digest Liver Dis, 2013;45(4):269-276.
54. Hart, AR, Luben, R, Olsen, A, Tjonneland, A, Linseisen, J, Nagel, G, Appleby, P. Diet in the aetiology of ulcerative colitis: a European prospective cohort study. Digestion, 2008;77(1):57-64.
55. Shivappa, N, Hébert, JR, Rashvand, S, Rashidkhani, B, Hekmatdoost, A. Inflammatory potential of diet and risk of ulcerative colitis in a case–control study from Iran. Nutr Cancer, 2016;68(3):404-409.
56. Li, F, Liu, X, Wang, W, Zhang, D. Consumption of vegetables and fruit and the risk of inflammatory bowel disease: a meta-analysis. Eur J Gastroenterol Hepatol, 2015;27(6):623-630.
57. Chiba, M, Abe, T, Tsuda, H, Sugawara, T, Tsuda, S, Tozawa, H, Imai, H. Lifestyle-related disease in Crohn's disease: relapse prevention by a semi-vegetarian diet. World J Gastroenterol WJG, 2010;16(20):2484.
58. Lee, D, Albenberg, L, Compher, C, Baldassano, R, Piccoli, D, Lewis, JD, Wu, GD. Diet in the pathogenesis and treatment of inflammatory bowel diseases. Gastroenterology, 2015;148(6):1087-1106.
59. Sakamoto, N, Kono, S, Wakai, K, Fukuda, Y, Satomi, M, Shimoyama, T, Kobashi, G. Dietary risk factors for inflammatory bowel disease A Multicenter Case-Control Study in Japan. Inflam Bowel Dis, 2005;11(2):154-163.
60. Geerling, BJ, Dagnelie, PC, Badart-Smook, A, Russel, MG, Stockbrügger, RW, Brummer, RJ. Diet as a risk factor for the development of ulcerative colitis. Am J Gastroenterol, 2000;95(4):1008-1013.
61. Qalqili T, Rayyan Y, Abu-Sneineh A, Tayyem R. Nutrients consumed by the inflammatory bowel disease Jordanian patients. Ann Cancer Res Ther, 2021;29(1):22-29.