Review Article

About the Pathogenesis of Inflammatory Bowel Disease - A Review

***Mia MR[1], Tajkia T[2], Khadiza D[3]**

Abstract

Inflammatory bowel disease (IBD) refers to a persistent inflammatory condition of the gut arising from interactions between the host's physiology and intestinal microbes in those with a genetic predisposition. This category of autoimmune disorders involvesinflammation of the intestinal tract, where the body's immune system targets components of its own digestive system. The development of IBD is multifactorial. Its worldwide prevalence is rising, prompting more individuals to consider dietary choices as both an explanatory factor and a therapeutic approach for their condition. Indeed, many patients are convinced that diet is crucial in triggering and controlling their IBD symptoms. Recent research has significantly advanced our understanding of IBD's underlying mechanisms, resulting in major progress in both its treatment and diagnosis. This review systematically examines the disease's pathogenesis and emphasizes current discoveries concerning host genetics, intestinal flora, the influence of diet and environmental triggers. These areas may provide vital insights for discovering new predictive or prognostic markers and creating innovative treatments.

PAH Med Col J. Jan 2025; 2(1): 27-34

Keywords: *Inflammatory bowel disease, Crohn's diesease, Ulcerative colitis, Diet*

Introduction

Inflammatory bowel disease (IBD) is a long-term inflammatory disorder of the digestive system, clinically encompassing Crohn's disease, ulcerative colitis and related diagnoses[1]. Crohn's disease can involve any part of the gastrointestinal tract from the mouth to the anus, while ulcerative colitis is typically confined to the colon and rectum[2,3,4]. Histologically, Crohn's disease exhibits transmural inflammation, whereas ulcerative colitis is limited to the mucosal layer of the gut lining[5]. IBD is a chronic condition often diagnosed in early adulthood, affecting both sexes[6]. Crohn's disease has a slight female predominance, but ulcerative colitis occurs equally in men and women. Geographically, IBD is more common in industrialized nations and regions with colder climates[7]. The occurrence and prevalence of IBD rose significantly during the latter half of the 20th century. In the 21st century, it has become one of the most common gastrointestinal disorders, with a rising incidence in newly industrialized nations[8,9,10]. Crohn's disease prevalence is notably elevated in highly developed countries, with an incidence of approximately 5 per 100,000 individuals and an estimated prevalence of, 30-50 per 100,000 in Western populations[11]. In Canada, for instance, about 129,000 individuals are affected[12]. While diagnosis typically happens in adulthood, pediatric cases are becoming more frequent. Since 1990, incidence rates in Western nations have stabilized or begun to decline, whereas rates in newly industrializing countries across Asia, Africa and South America continue to climb[10]. Although Crohn's disease and ulcerative colitis have overlapping features, differentiating between them can be challenging; they are distinguished by the specific sites and patterns of inflammation within the gut[11]. The exact etiology of IBD is still unclear, but substantial advances have recently been made in understanding its development. Research indicates that its pathogenesis is linked to genetic predisposition,

1.*Dr Mohammad Rajibe Mia, Associate Professor, Department of Endocrinology, President Abdul Hamid Medical College Hospital, Jafrabad, Karimganj, Kishoreganj

2.Dr Tanzina Tajkia, Associate Professor, Department of Physiology, President Abdul Hamid Medical College, Karimganj, Kishoregonj

3.Dr. Khadiza Diluara, Assistant Professor, Department of Biochemistry, President Abdul Hamid Medical College; Bangladesh.

Article History: Received: 03-04-2024 **Revised:** 23-04-2024 **Accepted:** 18-07-2024

Address of Correspondence: Dr Mohammad Rajibe Mia, Associate Professor, Department of Endocrinology, President Abdul Hamid Medical College Hospital, Jafrabad, Karimganj, Kishoreganj. E-mail:rajibemia06@gmail.com; CellNumber:01911567538

gut microbiome composition, additional environmental influences and immune system dysregulation[13,14].

Signs and symptoms of IBD

The intestinal lining inflammation in IBD presents with recurrent symptoms such as abdominal cramping, diarrhoea, bloody feces and loss of weight. This is driven by an infiltration of immune cells like neutrophils and macrophages, which release inflammatory signals, enzymes and reactive molecules that cause tissue damage and ulceration[1,15]. Clinical manifestations often differ based on the specific IBD form[16]. In ulcerative colitis, continuous mucosal inflammation leads to swelling, ulceration, hemorrhage and fluid-electrolyte imbalance. The inflammation typically begins in the rectum and spreads contiguously upward through the colon[7]. Affected individuals commonly report pain in the lower left abdomen alongside diarrhoea, which can lead to weight reduction and rectal bleeding[17,18].

Conversely, Crohn's disease more frequently causes discomfort in the lower right abdomen and visible rectal bleeding is less common than in ulcerative colitis. Afrequent complication is intestinal obstruction from pronounced swelling and bowel wall thickening. Additionally, malabsorption issues in Crohn's disease often result in nutritional deficits or malnutrition[17,18]. Crohn's disease can also lead to strictures, persistent inflammation, or fistula formation. Its hallmark pathological characteristic is

transmural involvement, meaning it affects the entire depth of the intestinal wall[7].

World Gastroenterology Organization (WGO) Diagnostic Criteria for IBD

i. Diarrhea, which can contain blood or mucus, often occurs nocturnally and involuntary stool leakage is frequently reported.

ii. Constipation may be a symptom in ulcerative colitis cases where inflammation is restricted to the rectal area.

iii. Other frequent symptoms include abdominal cramping, a constant feeling of needing to pass stool and intense, sudden urgency.

iv. Pain in the right lower abdomen is typical for Crohn's disease, while left lower quadrant pain is more common in ulcerative colitis.

v. Feelings of nausea and episodes of vomiting are observed more often in Crohn's disease than in ulcerative colitis.

Physical Exam

•Elevated heart rate, restlessness, pyrexia and fluid loss are frequently observed.

•Skin pallor may be apparent, correlating with the presence and degree of anemia.

•Toxic megacolon can manifest with intense pain, fever, abdominal bloating, rigors and profound fatigue. This critical surgical condition must always be considered, as it is life-threatening if not recognized.

•Individuals with Crohn's disease may present with perianal fistulae, abscesses, or rectal prolapse.

•A digital rectal examination commonly reveals hidden blood.

•In pediatric cases, the sole presenting sign may be a failure to achieve expected growth milestones.

Etiology

The etiology of IBD is still not fully understood. Multiple factors have been proposed, but no single cause is consistently identified in every case[7]. IBD is a multifactorial disorder triggered by a combination of genetic predisposition and environmental exposures, which then initiates an abnormal immune reaction and intestinal inflammation[2]. A well-established characteristic of Crohn's disease is its strong association with tobacco use. Conversely, smoking appears to reduce the risk of developing ulcerative colitis[7]. This is an example of a factor that differentially influences disease subtypes, exacerbating Crohn's disease while offering protection against ulcerative colitis[19,20]. Smoking has been demonstrated to alter both cellular and antibody-mediated immune functions and to stimulate mucus production in the colon[19,21]. Research also indicates that smoking disrupts autophagy, a cellular process believed to be particularly relevant in Crohn's disease pathogenesis[22]. The influence of diet continues to be asubject of debate[7]. A 2022 investigation concluded that dietary patterns emphasizing higher consumption of fruits and vegetables, lower intake of processed meats and refined carbohydrates and adequate hydration with water correlated with a decreased likelihood of active IBD symptoms. However, increasing fruit and vegetable intake alone did not lower symptom risk specifically for Crohn's disease[23].

Pathogenesis of IBD

1. Genetic Factors

Research utilizing genome-wide association studies (GWAS), next-generation sequencing and related methods has uncovered more than 240 distinct genetic regions associated with disease risk. Approximately 30 of these loci are common to both Crohn's diseaseand ulcerative colitis[24,25,26].

Examination of these genes and loci reveals that multiple biological pathwayscrucial for intestinal balance are involved, including the integrity of the epithelial barrier, innate immune defense at the mucosa, regulation of immunity, cellular movement, autophagy processes, adaptive immune responses and metabolic pathways linked to maintaining cellular stability[27,28,29,30]. Variations in the CARD15 gene are linked to IBD, but due to its polymorphic nature, predicting the specific segment of the gastrointestinal tract that will be affected is not possible. Genetic factors appear to play a less dominant role in ulcerative colitis compared to their influence in Crohn's disease[7].

2. Gut Microbial Factors

IBD is thought to develop from an aberrant immune reaction by the host to the microbes residing in the gut[31,32,33]. The intestinal microbiome acts as the primary environmental factor influencing IBD. From birth, the human digestive system is inhabited by an immense diversity of microorganisms, which outnumber the body's own cells by roughly tenfold[33,34]. Collectively, these microbes possess a gene repertoire approximately one hundred times larger than the human genome[31,33,34]. Factors such as diet, probiotic and prebiotic intake, antibiotic use, supplemental enzymes, fecal microbiota transplants and other external elements can alter the composition of this gut flora[32] .A balanced gut microbiota is essential for maintaining normal intestinal function, stability and overall health and is implicated in various disease states[33,34,35].

3. Environmental Factors

The significant influence of environmental factors on IBD development is reinforced by recent epidemiological research. The incidence of Crohn's disease has risen notably in industrialized nations over the last half-century and its identification has similarly grown in developing regions as they industrialize[36,37]. Diet is a key environmental element impacting IBD onset[38]. Evidence suggests that consuming fruits and vegetables correlates with a lower risk of Crohn's disease[39]. while diets high in fast food, fats and sugars may worsen its development[38]. High intake of protein, especially from animal sources and sugars may also be linked to an elevated risk of IBD and symptom recurrence[40,41]. Meat contains sulfur amino acids, which gut bacteria ferment to produce hydrogen sulfide. This compound may contribute to ulcerative colitis by interfering with butyrate metabolism in colon cells and weakening the intestinal mucus barrier, thereby increasing permeability to pathogens[42,43]. Research indicates that dietsrich in animal protein can promote pro-inflammatory immune cell responses and worsen colitis in animal models[44]. Dietary fats, particularly polyunsaturated fatty acids (PUFAs), have also been implicated in IBD pathogenesis[45]. Recently, emulsifiers- food additives used to improve texture and shelf life- have gained attention as potential inflammatory agents that may contribute to IBD[46]. They can alter the gut microbiome by reducing its diversity and encouraging pro-inflammatory bacteria. Common sources of emulsifiers include ice cream, plant-based milks, dressings and pasta[47,48,49]. A systematic review by Hou et al. generally found that higher dietary fiber intake was associated with reduced risk of both UC and CD, though only one study reported a statistically significant reduction for CD[50]. Fiber helps maintain gut barrier integrity by supporting the inner mucus layer, which contains antimicrobial compounds and acts as a defense against pathogens[51]. Fiber deprivation shifts the microbiome toward mucus-degrading bacteria and thins the protective mucus layer, bringing bacteria closer to the intestinal epithelium[52,53]. Overall, components like meat, fats, fiber and additives interact with the microbiome to either strengthen or compromise intestinal barrier function, influencing pathogen exposure. Many IBD patients modify their diets to manage symptoms, commonly avoiding spicy foods, dairy, fatty foods and high-fiber vegetables- often cited as "trigger" foods[54,55,56,57,58]. Alcohol is also reported to worsen symptoms but has been less consistently studied[54,56]. A survey of 2329 IBD patients found that those with active disease were more likely to avoid fruits, vegetables, tomatoes, beans and ice cream compared to those in remission[56]. Conversely, yogurt and rice were frequently reported to alleviate symptoms. Importantly, while certain foods may worsen gastrointestinal

symptoms, studies have not proven they increase underlying inflammation. Thus, individualized dietary adjustments can improve comfort even if they don't directly reduce inflammation. Other environmental factors linked to IBD include psychological stress, prior appendectomy and certain medications[59]. For instance, appendectomy is a risk factor for Crohn's disease but appears protective against ulcerative colitis[60]. Although epidemiological studies have identified these associations, understanding the precise mechanisms by which environmental factors influence IBD progression remains a challenge[59].

4.Immunological Abnormalities

The immune system's reaction to gut bacteria is precisely controlled, a process that dictates whether immune tolerance or a protective inflammatory reaction occurs. Disruption of this equilibrium can lead to IBD[61]. The gut-associated immune system plays acentral role in IBD's development. The intestinal lining normally blocks microbes and antigens from entering the bloodstream via tight cellular connections[7]. In IBD, these connections are impaired, either due to an intrinsic barrier defect or as a consequence of intense inflammation. Other defenses include mucus secreted by goblet cells and antimicrobial peptides like α-defensins released by Paneth cells. Excessive inflammation causes ongoing damage to the epithelial layer, increasing exposure to intestinalbacteria and creating a cycle of worsening inflammation[7]. The immune dysfunction in IBD involves multiple components: epithelial injury (including faulty mucus production and impaired healing); inflammation amplified by the gut flora and a heavy infiltration of immune cells- such as T cells, B cells, macrophages, dendritic cells and neutrophils- into the mucosal tissue; and a breakdown in the regulatory mechanisms needed to resolve the inflammatory response[8,62,63].

Diagnosis

Diagnosis typically involves evaluating fecal markers of inflammation, then proceeding to colonoscopy with tissue sampling from affected areas[64]. Confirmation is usually achieved through biopsy during colonoscopic examination. Measuring fecal calprotectinserves as a helpful initial test, as it can indicate the likelihood of IBD due to its high sensitivity, although it is not specific to the disease[65,66].

Histopathology

Histological examination in ulcerative colitis reveals inflammation confined to the mucosal and submucosal layers, featuring crypt abscesses and superficial ulcers. Tissue samples demonstrate infiltration by neutrophils, architectural distortion of the crypts and these characteristic abscesses. Granulomas are not present. The inflammation is continuous and almost always includes the rectum.

The formation of pseudo polyps is another typical finding. In Crohn's disease, inflammation affects the full thickness of the intestinal wall and may include granulomas. The inflammatory pattern is transmural and marked by a lymphocytic infiltrate[7]. Histologically, Crohn's disease shows a widened submucosa, transmural inflammation, fissuring ulcers and granulomas. By contrast, ulcerative colitis involves only the mucosa and submucosa, with cryptitis and crypt abscesses as hallmarks[67,68,69].

Complication

Ulcerative colitis increases the risk for complications outside the intestines, commonly affecting the skin, eyes and joints. These most frequently include inflammatory joint conditions and primary sclerosing cholangitis. Crohn's disease primarily targetsthe ileum and colon but can also involve the esophagus, stomach, or duodenum. Similar to UC, Crohn's is associated with systemic manifestations such as arthritis, mouth ulcers, uveitis, erythema nodosum and ankylosing spondylitis[70,71]. Research indicatesa higher mortality risk for individuals with Crohn's disease. Analyses focusing on intestinal cancers reveal that these patients also have increased comorbidities, including colorectal cancer, cardiovascular disorders and respiratory illnesses[17,18]. In Crohn's disease, kidney disorders and gallstones occur more frequently due to impaired absorption of bile acids and fatty acids. Patients who have had ileal resection while retaining their colon are also at greater risk for developing calcium oxalate kidneystones[7].

Conclusion

IBD is a persistent and potentially severe disorder marked by recurrent gut inflammation. Living with this condition can be difficult, though many affected individuals maintain a largely regular lifestyle. The diagnosis often carries a psychological weightdue to associated stigma, frequently resulting in elevated anxiety, depressive

symptoms and an overall decline in life quality. Significant advancements over recent decades have deepened our insight into IBD's mechanisms, particularly in immunology and have opened new avenues for therapeutic discovery. Nonetheless, unanswered questions remain regarding its origin, disease progression patterns and the specific triggers of inflammation across different patient subsets, necessitating further research. Theinteractions between pro-inflammatory and anti-inflammatory cells and signaling molecules, combined with various genetic predispositions, gut flora compositions and external factors (such as diet, tobacco use and stress), are under ongoing investigation. This work aims to build a complete picture of the disease process. With this growingunderstanding, we may be able to create innovative, tailored therapies for those with IBD.

References

1. Szigethy E, McLafferty L, Goyal A. Inflammatory bowel disease. Child and Adolescent Psychiatric Clinics of North America.2010;19(2):301-18.
2. Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet. 2007;369(9573):162740.
3. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet. 2007;369(9573): 1641-57.
4. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature. 2007;448(7152):427-34.
5. Ljung T, Karlén P, Schmidt D et al. Infliximab in inflammatory bowel disease: clinical outcome in a population-based cohort from Stockholm County. Gut. 2004;53:849-53.
6. Qingdong G. A Comprehensive Review and Update on the Pathogenesis of Inflammatory Bowel Disease. Journal of Immunology Research. 2019;2019.
7. McDowell C, Farooq U, Haseeb M. Inflammatory Bowel Disease. In: Stat Pearls. Treasure Island (FL): Stat Pearls Publishing; 2023 Jan.
8. Korzenik JR, Podolsky DK. Evolving knowledge and therapy of inflammatory bowel disease. Nature Reviews Drug Discovery. 2006;5(3):197-209.
9. Hanauer SB. Inflammatory bowel disease: epidemiology, pathogenesis and therapeutic opportunities. Inflammatory Bowel Disease. 2006;12(Suppl 1):S3-S9.
10. Ng SC, Shi HY, Hamidi N et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2018;390(10114):2769-78.
11. Cassinotti A, Ardizzone S, Porro GP. Adalimumab for the treatment of Crohn's disease. Biologics. 2008;2:763-77.
12. Sandborn WJ, Feagan BG, Lichtenstein GR. Medical management of mild to moderate Crohn's disease: evidence-based treatment algorithms for induction and maintenance of remission. Aliment Pharmacol Ther. 2007;26: 987-1003.
13. Monteleone G, Fina D, Caruso R, Pallone F. New mediators of immunity and inflammation in inflammatory bowel disease. Current Opinion in Gastroenterology. 2006;22(4):361-4.
14. Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. Annual Review of Immunology. 2010;28(1):573-621.
15. Stokkers PC, Hommes DW. New cytokine therapeutics for inflammatory bowel disease. Cytokine. 2004;28(4-5):167-73.
16. Marc F, Rebecca N, Armin M, Hani S. Inflammatory bowel disease: clinical aspects and treatments. Journal of Inflammation Research. 2014;7:113-20.
17. Canavan C, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease.Aliment Pharmacol Ther. 2006;23:1097-1104.
18. Jess T, Gamborg M, Matzen P, Munkholm P, Sørensen TI. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. Am J Gastroenterol. 2005;100:2724-29.
19. Ardizzone S, Bianchi Porro G. Biologic therapy for inflammatory bowel disease. Drugs. 2005; 65(16):2253-86.
20. Lakatos PL. Environmental factors affecting inflammatory bowel disease: have we made progress? Digestive Diseases. 2009;27(3):215-25.
21. Hibi T, Ogata H. Novel pathophysiological concepts of inflammatory bowel disease. The Journal of Gastroenterology. 2006;41(1):10-6.
22. Monick MM, Powers LS, Walters K et al. Identification of an autophagy defect in

smokers' alveolar macrophages. Journal of Immunology. 2010;185(9):5425-35.
23. Limketkai NB, Hamideh M Shah R, Jenny S, Jaffe N. Dietary Patterns and Their Association with Symptoms Activity in Inflammatory Bowel Diseases. Inflammatory Bowel Diseases. 2022;28(11):1627-36.
24. Mirkov MU, Verstockt B, Cleynen I. Genetics of inflammatory bowel disease: beyond-NOD2. The Lancet Gastroenterology & Hepatology. 2017;2(3):224-34.
25. Huang H. International Inflammatory Bowel Disease Genetics Consortium. M. Fang et al. Fine-mapping inflammatory 10 Journal of Immunology Research bowel disease loci to single-variant resolution. Nature. 2017;547 (7662):173-8.
26. Peters LA, Perrigoue J, Mortha A et al. A functional genomics predictive network model identifies regulators of inflammatory bowel disease. Nature Genetics, 2017;49(10):1437-49.
27. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011;474(7351)307-17.
28. Mehta M, AhmedS, Dryden G. Immuno-pathophysiology of inflammatory bowel disease: how genetics link barrier dysfunction and innate immunity to inflammation. Innate Immunity. 2017;23(6):497-505.
29. Liu TC, Stappenbeck TS. Genetics and pathogenesis of inflammatory bowel disease. Annual Review of Pathology. 2016;11(1):127-48.
30. Cohen LJ, Cho JH, Gevers D, Chu H. Genetic Factors and the Intestinal Microbiome Guide Development of Microbe-Based Therapies for Inflammatory Bowel Diseases. Gastroenterology. 2019;156(8):2174-89.
31. Nishida A, Inoue R, Inatomi O, Bamba S, Naito Y andoh. Gut microbiota in the pathogenesis of inflammatory bowel disease. Journal of Clinical Gastroenterology. 2018;11(1):1-10.
32. Richard ML, Sokol H. The gut mycobiota: insights into analysis, environmental interactions and role in gastrointestinal diseases. Nature Reviews Gastroenterology & Hepatology. 2019; 16(6):331-45.
33. Saleh M, Elson CO. Experimental inflammatory bowel disease: insights into the host-microbiota dialog. Immunity. 2011;34(3): 293-302.
34. Nell S, Suerbaum S, Josenhans C. The impact of the microbiota on the pathogenesis of IBD: lessons from mouse infection models. Nature Reviews Microbiology. 2010;8(8):564-77.
35. Zuo T, Kamm MA, Colombel JF, Ng SC. Urbanization and the gut microbiota in health and inflammatory bowel disease. Nature Reviews Gastroenterology & Hepatology. 2018;15(7):440-52.
36. Ardizzone S, Bianchi Porro G. Biologic therapy for inflammatory bowel disease. Drugs. 2005; 65(16):2253-86.
37. Lakatos PL. Environmental factors affecting inflammatory bowel disease: have we made progress? Digestive Diseases. 2009;27(3):215-25.
38. Hibi T, OgataH. Novel pathophysiological concepts of inflammatory bowel disease. The Journal of Gastroenterology. 2006;41(1):10-6.
39. Dolan KT, Chang EB. Diet, gut microbes and the pathogenesis of inflammatory bowel diseases. Molecular Nutrition & Food Research. 2017;61(1).
40. Andersen V, Olsen A, Carbonnel F, Tjønneland A, Vogel U. Diet and risk of inflammatory bowel disease. Digestive and Liver Disease. 2012;44(3):185-94.
41. Barron M. Sugar may trigger inflammatory bowel disease by breaking down gutmucus. Massive Science. 2021.
42. Roediger WE, Duncan A, Kapaniris O et al. Reducing sulfur compounds of the colon impairs colonocyte nutrition: implications for ulcerative colitis. Gastroenterology. 1993;104:802-9.
43. Ijssennagger N, Belzer C, Hooiveld GJ et al. Gut microbiota facilitates dietary heme-induced epithelial hyperproliferation by opening the mucus barrier in the colon. Proc Natl Acad Sci USA. 2015;112:10038-43.
44. Kostovcikova K, Coufal S, Galanova N et al. Diet rich in animal protein promotes pro-inflammatory macrophage response and exacerbates colitis in mice. Frontiers in Immunology. 2019:10.
45. Ananthakrishnan AN, Khalili H, Konijeti GG et al. Long-term intake of dietary fatand risk of ulcerative colitis and Crohn'sdisease. Gut. 2014;63:776-84.

46. Roberts CL, Rushworth SL, Richman E et al. Hypothesis: increasedconsumption of emulsifiers as an explanation for the rising incidence of Crohn's disease. J Crohns Colitis. 2013;7:338-41.
47. Chassaing B, Koren O, Goodrich JK et al. Dietary emulsifiers impact the mouse gut microbiota, promoting colitis and metabolic syndrome. Nature. 2015;519:92-6.
48. Shang Q, Sun W, Shan X et al. Carrageenan-induced colitis is associated with decreased population of anti-inflammatory bacterium, Akkermansia muciniphila, in the gut microbiota of C57BL/6J mice. Toxicol Lett. 2017;279:87-95.
49. Viennois E, Merlin D, Gewirtz AT et al. Dietary emulsifier-induced low-grade inflammation promotes colon carcinogenesis. Cancer Res. 2017;77:27-40.
50. Amre DK, Souza SD, Morgan K et al. Imbalances in dietary consumption of fatty acids, vegetables and fruits are associated with risk for Crohn's disease in children. Am J Gastroenterol. 2007;102:2016-25.
51. McGuckin MA, Linden SK, Sutton P et al. Mucin dynamics and enteric pathogens. Nat Rev Microbiol. 2011;9:265-78.
52. Desai MS, Seekatz AM, Koropatkin NM et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. Cell. 2016;167:1339-53.
53. Earle KA, Billings G, Sigal M et al. Quantitative imaging of gut microbiota spatial organization. Cell Host Microbe. 2015;18:478-88.
54. Limdi JK, Aggarwal D, McLaughlin JT. Dietary practices and beliefs in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2016;22:164-70.
55. Zallot C, Quilliot D, Chevaux JB et al. Dietary beliefs and behavior among inflammatory bowel disease patients. Inflamm Bowel Dis. 2013;19: 66-72.
56. Cohen AB, Lee D, Long MD et al. Dietary patterns and self-reported associations of diet with symptoms of inflammatory bowel disease. Dig Dis Sci. 2013;58:1322-8.
57. deVries JHM, Dijkhuizen M, Tap P et al. Patient's dietary beliefs and behaviours in inflammatory bowel disease. Dig Dis. 2019; 37:131-9.
58. Jowett SL, Seal CJ, Phillips E et al. Dietary beliefs of people with ulcerative colitis and their effect on relapse and nutrient intake. Clin Nutr. 2004;23:161-70.
59. Ho SM, Lewis JD, Mayer EA et al. Challenges in IBD research: environmental triggers. Inflammatory Bowel Disease. 2019;25 (Supplement_2):S13-S23.
60. Engel MA, Neurath MF. New pathophysiological insights and modern treatment of IBD. The Journal of Gastroenterology. 2010;45(6):571-83.
61. Abraham C, Cho JH. Inflammatory bowel disease. The New England Journal of Medicine. 2009;361(21):2066-78.
62. Choy MC, Visvanathan K, De Cruz P. An overview of the innate and adaptive immune system in inflammatory bowel disease. Inflammatory Bowel Disease. 2017;23(1):2-13.
63. Ince MN, Elliott DE. Immunologic and molecular mechanisms in inflammatory bowel disease. Surgical Clinics of North America. 2007;87(3):681-96.
64. Aydoğdu M, Gürsel G, Özyilmaz E, Akyürek N, Memış L. A case of ulcerative colitis complicated with bronchiolitis obliterans organizing pneumonia (BOOP) and air leak syndrome. The Turkish Journal of Gastroenterology. 2012;23(5):590-5.
65. Henderson P anderson NH, Wilson DC. The diagnostic accuracy of fecalcalprotectin during the investigation of suspected pediatric inflammatory bowel disease: a systematic review and meta- analysis. The American Journal of Gastroenterology. 2014;109(5):637-45.
66. Waugh N, CumminsE, Royle P, Kandala NB, Shyangdan D, Arasaradnam R et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. 2013.
67. Abraham C, Cho JH. Inflammatory bowel disease. The New England Journal of Medicine. 2009;361(21):2066-78.
68. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011;474(7351):307-17.
69. Gajendran M, Loganathan P, Catinella AP, Hashash JG. A comprehensive review and update on Crohn's disease. Disease-a-Month. 2018;64(2):20-57.

70. Sturm A, Maaser C, Calabrese E et al., European Crohn's and Colitis Organization [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR] ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 2: IBD scores and general principles and technical aspects. J Crohns Colitis. 2019;13(3): 273-84.
71. Trivedi PJ, Adams DH. Chemokines and Chemokine Receptors as Therapeutic Targets in Inflammatory Bowel Disease: Pitfalls and Promise. J Crohns Colitis. 2018;12(suppl_2): S641-S652.