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Crohn's disease: Etiology, pathogenesis and treatment strategies

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ABSTRACT

Crohn's disease (CD), which can be localized in any part of the gastrointestinal tract, is a disease characterized by an irregular immune response to normal and/or abnormal microbial antigens. Recent studies show many extensive data about the roles of genetic and environmental factors, immune function, and gut microbiota in CD. Although, less invasive biomarkers are currently being developed, the diagnosis of the disease is still based on the endoscopy and histological evaluation of biopsy samples. The most common symptoms are diarrhea, abdominal pain, weight loss, and fatigue. Despite the improvements in the treatment methods in the last decade, there is no definitive treatment since the etiology of CD is not known exactly. Therapeutic strategies focus on reducing inflammation and symptoms, maintaining clinical remission, and improving quality of life.

Keywords: Crohn's Disease, Inflammatory bowel disease, Intestinal microbiota, Nutrition therapy

1. INTRODUCTION

Inflammatory bowel disease (IBD) represents a group of intestinal disorders including Crohn's disease (CD) and ulcerative colitis (UC) with clinical, epidemiological and pathological findings. It is characterized by acute and chronic inflammation of the gastrointestinal tract with unknown etiology [1]. Although, it is known as a disease of western societies, the incidence of IBD has increased rapidly in newly industrialized countries since the beginning of the 21st century [2]. It is estimated that currently, approximately nearly 3.9 million females and nearly 3.0 million males are living with IBD worldwide and the number of prevalent cases is on the rise [3]. In Turkey, the incidence of IBD has been reported as 1.4/100000 for CD and 2.6/100000 for UC, while its prevalence has been reported as 130/100000 and 100/100000, respectively [4, 5]. Both forms of IBD share similar clinical features including diarrhea, fever, weight loss, anemia, food intolerance, malnutrition, growth retardation, and extraintestinal situations such as arthritis, dermatologic and hepatic findings [4]. CD is an inflammatory condition of the gastrointestinal tract with focal, asymmetric, and transmural involvement that can occur anywhere between the mouth and the anus. On the other hand, UC is characterized by recurrent inflammation of the colonic sections limited to the mucosa [6]. In this review, the etiology, pathogenesis and treatment strategies of CD will be discussed in detail with updated information.

2. DIAGNOSIS and CLASSIFICATION

The first step in diagnosis of CD requires a detailed history (including family, social and medical) and physical examination. If CD has been potentially diagnosed, laboratory findings such as erythrocyte sedimentary rate, C-reactive protein, and leukocyte and platelet counts are examined [7]. Medical imaging can be used to confirm the diagnosis and to monitor the disease activity. Endoscopy procedure is useful to directly view the affected areas, to determine the degree of disease involvement, and for biopsy [8]. Intestinal biopsy is confirmatory rather than diagnostic [5]. Endoscopic biopsy is important to differentiate the CD from UC and to exclude acute colitis, dysplasia, or cancer [9].

Crohn's disease is clinically divided into 3 phenotypic subclasses; inflammatory, fistulizing, and obstructive. In the inflammatory subtype, diarrhea, abdominal pain, weight loss, and fever are the prominent findings. In the fistulizing subtype, intraabdominal mass, abscess, and fistula are common findings. As a result of immune activation, tissue destruction, sinus canal formation,

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and consequently penetration into neighboring tissue develop. Thus, fistulas are formed between the two segments of the gastrointestinal tract. If the inflammation spreads to the surrounding tissues and organs and remains enclosed, an abscess develops. In the obstructive subtype, as a result of prolonged inflammation, a stenosis due to fibrosis may occur in any segment of the intestine. Postprandial pain, bloating, and vomiting are seen in such patients. Strictures due to fibrostenosis can lead to complete obstruction [10].

3. CLINICAL FINDINGS and SYMPTOMS

Crohn's disease mainly affects the ileum and cecum in more than half of the cases. In patients with CD, involvements are 15%, 20% and 15% in the small intestine, colon and anorectal area, respectively. The characteristic feature of CD is granulomatous intermittent lesions surrounded by sharply demarcated, normal-appearing mucosal tissue. Although, the retained layer is submucosa, all layers of the intestine are involved. The intestinal surface has the characteristic of "cobblestone" appearance arising from clefts and cracks surrounded by submucosal edema areas. Marked inflammatory and fibrotic changes occur in the submucosal layer. Intestinal smooth muscles are relatively less involved. After a while, the intestinal wall thickens and usually loses its flexibility [8].

Crohn's disease is a slowly progressive and aggressive disease with high morbidity [8]. Diarrhea, abdominal pain, rectal bleeding, fever, weight loss, and fatigue are the most common symptoms [11]. Because of the stimulation of pain receptors (located in the serosa and peritoneum) due to transmural bowel involvement, abdominal pain occurs more frequently in patients with CD than patients with UC [5]. Also, perianal ulceration is prevalent due to diarrhea. Since, CD affects the submucosal layer rather than the mucosal layer, bloody diarrhea is less common in patients with CD compared to patients with UC [8].

Although, the course of the disease is different in most patients, perforation, fistula, abscess, and small bowel obstruction are the most common complications of CD [8, 12].Additionally, an increase in cancer incidence is observed in CD patients [13]. Patients may have inflammatory disorders other than the gastrointestinal system such as arthritis (joints), erythema nodosum (skin), uveitis and iritis (eye), epithelial mucosa aphthous ulcers (mucous membrane), sclerosing cholangitis (bile ducts), and cirrhosis (liver) [12, 13]. Renal disorders such as nephrolithiasis due to an increase in oxalate absorption associated with steatorrhea were found in 1/3 of the patients with CD. Amyloidosis and thromboembolic disease which indicate systemic inflammation, are serious complications of CD [12]. Also, malnutrition is frequently observed in patients with CD [8, 12].

4. ETHIOLOGY

Genetic Factors

Crohn's disease is considered as a multifactorial disease resulting from the effect of both environmental and genetic components on the gut microbiome. Differences in occurrence, severity and complications of disease, areas of involvement and differences in treatment response can be explained by the genetic dissimilarities between individuals [4].

Approximately, 200 risk loci for IBD have been identified so far with the development of molecular genetic techniques. However, only a few genes (CARD15, NOD2, ATG16L1, IRGM, LRRK2, PTPN2, IL23R, Il10, Il10RA, Il10RB, CDH1, and HNF4A) have been extensively studied and a strong relationship between these genes and IBD has been idendified [4, 14]. CARD15 and NOD2 gene mutations have shown the strongest association with CD (35-45% of cases) compared to other genes. The CARD15 and NOD2 genes encode a protein (a toll-like receptor) involved in the recognition of gram-negative and gram-positive bacterial wall fragments by intestinal epithelial cells. Therefore, mutations in the CARD15 and NOD2 genes may increase dysbiosis [15]. It is believed that a gene panel including key genes will contribute to the diagnosis and evaluation of IBD in the future [14].

Environmental Factors

Among the CD risk factors, smoking was researched most extensively and it doubles the risk of disease development especially at an early age [16]. It is also associated with increased severity of disease and is thought to cause resistance to treatment [17]. It was observed that the progression of the disease and the need for surgery have been decreased when patients with CD quit smoking [18]. Although the mechanisms underlying the link between smoking and CD are not completely understood, changes in the immune system, abnormal cytokine levels, and changes in intestinal permeability and motility are thought to be involved in the CD development [19].

It has been shown that diets rich in sugar, omega-6 fatty acids, polyunsaturated fatty acids, fat, and meat (except fish) increase the risk of CD, while fiber-rich plant-based diets reduce the risk of CD [20-22]. Antibodies against milk proteins and baker's yeast *Saccharomyces cerevisiae* have been detected in patients with CD [4]. Besides, it has been stated that low intakes of zinc and vitamin D and high iron intake may play a role in the development of CD [23]. However, it is difficult to interpret the findings as nutrition studies generally have poor research methods. Therefore, the role of nutrition in the development of CD has not been fully understood, further studies with high sample sizes are needed.

Oral contraceptive pills have also been associated with the development of CD, especially among smokers [24]. Additionally, non-steroidal anti-inflammatory drugs have been reported to trigger exacerbations in IBD [25].

Hygiene hypothesis associated with the prevalence of autoimmune diseases may also be the cause of IBD. It has been found that living in rural areas, having a large number of siblings, drinking unpasteurized milk, and exposure to domestic animals during in early childhood are inversely proportional to the risk of CD or UC [26].

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Although, there are no strong evidences, *Mycobacterium paratuberculosis*, *Pseudomonas* spp. and *Listeria* spp. are all suggested as possible causes for CD [27].

Since, CD is more common in northern latitudes where sun exposure is less, it is thought to be associated with vitamin D deficiency [25].

There is a growing body of research supporting the relationship between psychiatric diseases and development of IBD [28, 29].

5. PATHOGENESIS

In a healthy intestine, a mild inflammatory response is created against microbial agents, on the other hand, this situation is disrupted in CD and leads to uncontrolled inflammation [12]. It has been reported that various disturbances in the immune pathways may cause uncontrolled inflammatory cascades [7]. These disturbances are associated with the intestinal barrier function, innate and adaptive immune responses, and gut microbiota (Figure 1).

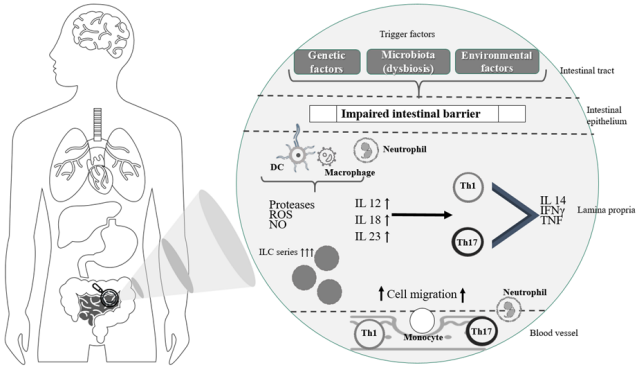

Figure 1. *Pathophysiology of Crohn's Disease.*
DC: Dendritic cell; ILC: Innate lymphoid cell; Th: T helper cell; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon, ROS: Reactive oxygen species; NO: Nitric oxide

Intestinal Barrier Function

The intestinal epithelium which is located between the gut microbiome and the wall of the gastrointestinal tract, prevents entry of bacteria and plays an important role in generating the mucosal immune response. Also, a healthy mucosal barrier includes tight junctions of the epithelial cells. Other defense mechanisms of the gastrointestinal tract include various specialized intestinal epithelial cells such as goblet cells that help to control mucus production, epithelial repair and inflammation, and Paneth cells that secrete antimicrobial peptides [8]. Intestinal epithelial cells are the first line of defense mechanism of the mucosal immune system [10]. Epithelial permeability is increased in patients with CD which allows pathogens to pass through the mucosal layers [7]. Numerous environmental factors, such as microbial pathogens, can trigger the immune response, generate endoplasmic reticulum stress, elicit a misfolded protein response, and initiate the inflammatory cascade [13]. Epithelial cells have inhibitory functions that destroy unwanted cytoplasmic contents by autophagy and prevent spread of invasive bacterial species [30]. Defects in autophagy-dependent genes, such as ATG16L1 and IRGM, have been identified as important risk factors for CD [31]. Defects in intestinal tight junctions are also associated with IBD [13].

Immune Responses

Leukocytes which are located in the intestinal epithelium, have an important role in maintaining homeostasis. T cells, a group of leukocyte members, play a primary role in cell mediated immunity. It has been found that there is an excessive increase in T helper (Th) 1 and Th17 cell responses against proinflammatory cytokines such as interleukin (IL)-12, IL-18 and IL-23 produced by macrophages and antigen presenting intestinal leukocyte cells in CD [31]. Th1 and Th17 cells secrete proinflammatory cytokines such as IL-17, interferon (IFN)-γ ve tumor necrosis factor (TNF)-α, and these cytokines induce production of TNF-α, IL-1, IL-6, IL-8, IL-12 and IL-18 from other cells such as macrophages, monocytes, endothelial and dendritic cells located in lamina propria to sustain inflammation [32, 33]. Thus, mucosal inflammation and damage to the epithelial barrier are accelerated. Furthermore, intestinal damage gradually increases with the release of proteases and reactive oxygen species from leukocytes and with the production of nitric oxide. When increasing numbers of migrated neutrophils to inflammed tissue invade and destroy the intestinal crypts, aphthoid lesions (shallow ulcers) occur [34].

The stimulation of inherited pattern recognition receptors (PRRs) contributes to this inflammatory response in the organism. PRRs recognize microbial pathogen-related molecular patterns and show an immune reaction to substances secreted by the organism itself under stress conditions such as tissue damage and necrotic cell death. PRRs are divided into many subtypes. Among these, the best described receptors are toll-like receptors (TLRs). Ten (TLR1-TLR10) and 12 (TLR1-TLR9, TLR11-TLR13) different TLRs have been identified in humans and mice, respectively [35]. TLR2 recognizes most of the intestinal microbes that make up the natural bacterial flora of the gut. A decrease in the number of TLR3 and TLR5 due to decreased expression was found in patients with CD. This situation can aggressively induce an inflammatory response with the formation of hypersensitivity to commensal exposure [7].

Gut Microbiota

Microbiota is thought to play an important role in the pathogenesis of CD. Dysbiosis is seen in the gut microbiota of IBD patients and is characterized by a decrease in microbial diversity compared to healthy individuals. This reduction in microbial diversity is more pronounced for CD than UC [26]. Dysbiosis is characterized by a decrease in *Bacteroides* and *Firmicutes* bacteria, and an increase in *Gammaproteobacteria* and *Actinobacteria* in patients with CD [36]. Besides, *Faecalibacterium prausnitzii*, which is responsible for the production of an anti-inflammatory protein that inhibits the nuclear factor (NF)-κB pathway, has also been found to be reduced in patients with CD [37].

Patients with CD have a higher number of mucosal surface-associated bacteria (such as adhesive-invasive *Escherichia coli*) due to increased adhesion and invasion compared to healthy controls [38]. These invasive strains cross the mucosal barrier, adhere to the intestinal epithelial cells and trigger the secretion of increased amounts of TNF-α from the macrophages [38, 39].

The intestinal microbiota is diverse and unstable in early childhood. Disruption of this microbiota in early childhood may affect the gut immune response, alter the sensitivity to IBD, and this sensitivity is greater for CD [40]. It has been found that the use of antibiotics, especially in early childhood, increases the risk of CD development more than the use in later periods [41]. Stress, air pollution, hygiene and diet are other factors that affect the composition and functional activity of the gut microbiota. Since the effect of diet on microbial composition is transient, its effect on changed microbial diversity in CD is controversial [13]. As a result, all these factors cause the proliferation of pathogen-specific T cells in addition to the commensal specific effector-T cells that have been temporarily formed in the mucosal barrier [34].

6. TREATMENT STRATEGIES

Despite the advances in treatment methods in the last decade, there is no definitive treatment because the etiology of CD is not completely understood. Therapeutic strategies focus on alleviating and reducing inflammation and symptoms [42]. Smoking cessation is a component of treatment [34].

Medical treatment includes corticosteroids, 5-aminosalicylates, and immunomodulatory agents such as thiopurines and TNF-α blockers [34]. Also, new biological agents are being developed [43]. Options for the treatment of refractory patients include azathioprine, 6-mercaptopurine, methotrexate, and biological therapies [34].

Surgical treatment is usually performed to manage complications such as stenosis, fistula, abscess, and perforation in the gastrointestinal canal or to remove the obstruction. Surgical resection of small bowel segments can reveal complications associated with short bowel syndrome which include malabsorption, diarrhea, and nutrient deficiencies. Symptoms are related to the size and location of resection [34].

Recently, fecal microbiota transplantation (FMT) which is applied to increase microbial diversity, has become a potentially alternative therapeutic strategy for IBD to eliminate dysbiosis of the intestinal microbiota [43, 44]. There are still no definitive findings regarding the timing and frequency of FMT treatment and, the route of administration. Although significant side effects of the FMT treatment were not found in the clinical studies, it has been shown that there are unwanted immunological, physiological or metabolic phenotype transfers in animal studies [6]. In a study, clinical remission was achieved with the FMT treatment at the 12th week in 5 out of 9 patients with the age of 12-19 years [45]. In a case report, clinical remission and endoscopic recovery were achived after a single FMT infusion in a patient with CD who had previously failed biological therapy [44]. Prospective randomized controlled studies are needed to evaluate the safety and efficacy of FMT in IBD patients.

Table I. *The principles of medical nutrition therapy for Crohn's Disease (CD).*

	Ref.
According to the European Society for Clinical Nutrition and Metabolism (ESPEN) practical guideline, the energy requirements of patients with inflammatory bowel disease (IBD) are similar to those of the healthy population.	[48]
Protein consumption of 1.2-1.5 g/kg/day is recommended to prevent catabolism and to meet the protein requirement. The protein requirements in remission are similar (1g/kg/d) to that recommended for the healthy adults.	[48]
Simple carbohydrate consumption should be limited. If the individual has not developed lactose intolerance, lactose consumption does not create a risk. Excessive consumption of fructose or sorbitol can cause abdominal pain, gas, and diarrhea, so that, dietary intake of them should be considered.	[4]
Daily energy of 20-25% and 25-30% for patients should be met from fats in an active period and in a remission period, respectively. Since too much restriction of fat intake can lead to a deficiency of fat-soluble vitamins, attention should be paid to the pattern of fatty acids in the diet rather than fat restriction. High-fat diets can trigger an increase in steatorrhea. In the case of fat malabsorption, the use of medium-chain triglycerides may be beneficial in providing energy and fat-soluble vitamins.	[9]
The European Crohn's and Colitis Organisation recommends a temporary, low-fiber diet for most patients during an exacerbation period of the disease. Organisation recommends consuming as much pulp as needed by a healthy individual in the remission period.	[49]
Patients with IBD should be checked for micronutrient deficiencies on a regular basis and specific deficits should be appropriately supplemented.	[48]
There is no specific 'IBD diet' that can be generally recommended to promote remission. Exclusion diets are not recommended to achieve remission in active CD, even if the patient suffers from individual intolerances. Meals can be tolerated better with less and frequent feeding.	[48]
If oral feeding is not sufficient then EN should be considered as supportive therapy. In CD patients with intestinal strictures or stenosis in combination with obstructive symptoms, a diet with adapted texture, or distal (post-stenosis) EN is advised. EN in CD should be administered via an enteral feeding pump. EN should always take preference over PN, unless it is completely contraindicated.	[48]
No significant benefit for probiotics and prebiotics has been demonstrated in induction and maintenance of remission during the CD exacerbation period. Since probiotic supplements are found to be ineffective in CD, they are not recommended in updated ESPEN guidelines. On the other hand, they may be beneficial in some cases in ulcerative colitis patients.	[48, 50]
Patients with IBD are at risk and therefore should be screened for malnutrition.	[48]

The area and length of involvement in CD, the frequency and duration of the active period of the disease significantly affect the absorption disorder and nutrient deficiency. It causes abdominal pain, nausea, vomiting, diarrhea, and loss of fluid-electrolytes, vitamins and trace elements in exacerbation periods of the disease, and it also accelerates weight loss by reducing food intake and appetite [46]. Therefore, the primary

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goal in the medical nutrition treatment of CD is to improve and maintain the nutritional status and to maintain remission [4]. For this purpose, foods, nutritional supplements, enteral and parenteral nutrition methods can be used according to the period and severity of the disease [47]. IBD needs good nutritional follow-up and treatment to prevent malnutrition, to eliminate micronutrient deficiencies, to prevent osteoporosis. In patients diagnosed with IBD, it is essential to conduct routine screening for iron and folate deficiencies throughout pregnancy, along with nutritional follow-up [48]. The principles of medical nutrition therapy for CD are summarized in Table I.

Conclusion

Crohn's disease is a common disease with high morbidity in the world. Numerous genetic and environmental factors are associated with the development of CD. The importance of genetic factors, especially CARD15 and NOD2 gene mutations, is pointed out. Also, dysbiosis plays a crucial role in the development of the disease and in the effectiveness of treatment. Smoking, antibiotic exposure in early childhood, and western-style eating habits are important environmental factors in the etiology of the disease. In recent years, significant advances have been made in understanding the role of intestinal inflammation in CD pathogenesis. These advances have contributed to the examination of new therapeutic approaches such as FMT that can be preferred instead of current medical and surgical treatment strategies or it can support the existing treatments. Medical nutrition therapy is prominent in preventing symptoms such as diarrhea and abdominal pain which are common in patients with CD, and in maintaining remission. The use of probiotics in medical nutrition therapy has shown conflicting results, further studies are needed on this subject.

Compliance with Ethical Standards

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