



Current Approaches to Crohn's Disease Including COVID-19

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Abstract

Crohn's disease is a recurrent, chronic inflammatory disease of the gastrointestinal tract with an increasing worldwide prevalence. This disease is due to a complex interaction between genetic susceptibility, environmental factors and altered gut microflora. It significantly affects the morbidity and quality of life of individuals from all age groups from childhood to old age. Although genetic and environmental factors increase the risk of this disease, its etiology is unknown. Ileocolonoscopy examination and biopsy have been determined as the first step diagnosis. Computed tomography and magnetic resonance imaging are performed when these methods cannot be diagnosed. Since it is usually diagnosed during adolescence, stunted growth is the most important complication for the pediatric patient group. While various drugs are used in the treatment of the disease, corticosteroids are most commonly preferred. In Crohn's disease, nutrient deficiencies are usually seen as a result of oral intake. For this reason, the risk of malnutrition is high in Crohn's patients. According to ESPEN and British Society; in order to meet the energy and nutrient needs of the patients, nutritional support treatment should be done by considering the clinical condition of the patients. Individuals with Crohn's disease, immunosuppressant drugs may be at risk of COVID-19 due to chronic inflammatory symptoms and resulting nutrient deficiencies. As a result, lowering the risk of malnutrition in Crohn's disease and preventing nutrient deficiencies can improve the immune system by positively affecting the patient's quality of life.

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Introduction

Major Inflammatory Bowel Diseases (IBD), Crohn's disease and ulcerative colitis. Crohn's Disease (CD), it is a chronic inflammatory disease that can affect any part of the gastrointestinal tract from the mouth to the anus, leading to recurrent bowel damage [1,2]. All gastrointestinal system segments may be affected but the most affected parts of the intestine are colon and terminal ileum [3,4]. It usually occurs with clinical signs of abdominal pain, fever, intestinal obstruction or diarrhea, or both, with blood and mucus passage [5].

Epidemiology

CD can affect people from all ages. It has a negative impact on patients' morbidity and quality of life [1]. The disease is more common in industrialized countries, especially North America and Western Europe. However, the incidence of the disease is gradually increasing in Asia and South America. The prevalence of CD is between 3 and 20 cases per 100,000. The incidence may be slightly higher in women [6]. There are gender differences in various demographic characteristics. In the Canadian and New Zealand population, women are reported to be 10-



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30% more likely to get the disease than men, while in Japan and Korea, men are three times more likely to get the disease than women [7]. Since low-risk countries such as Japan, China and India have adopted the western lifestyle, the incidence of CD has clearly increased [4]. Rapid changes in the epidemiology of CD are a global challenge for disease diagnosis, healthcare, and disease prevention. In the newly industrialized countries (as in Asia), the increasing incidence of CD reflects the influence of Western lifestyle, especially diet, urbanization and industrialization [8].

Risk factors

Approximately 12% of the patients have a family history of CD. As only 13.1% of the disease inheritance is explained by genetic factors, non-genetic environmental factors and epigenetic factors also have significant effects on CD risk [4,8]. Despite all studies, only the genetic disease variance and phenotypes of CD could not be explained. Therefore, it is not used in genetic and clinical applications [4].

Smoking doubles the risk of developing CD [4,6]. Smoking has been identified as the only changeable risk factor for CD in Western countries. Some meta-analyses have revealed a difference in the effect of smoking on CD risk between different ethnicities. Passive smoking in Japan has also been associated with an increased risk of developing CD [8]. Exposure to antibiotics during early life has been associated with an increased risk of developing CD [6]. Factors such as breastfeeding, farm life and childhood contact with animals are protective factors against CD [4]. On the other hand, it has been observed that CD is triggered by changes in the intestinal microbiome or disruption in the intestinal mucosa. Despite research, the mechanisms of changes in the intestinal microbiome regarding the etiology of Crohn's disease are still not fully understood [6].

Etiology and pathogenesis

Although the etiology of CD is not known clearly, it is a complex interaction between genetic predisposition, environmental risk factors, and an imbalance of the gut microbiota [6,7]. Inflammation of the gastrointestinal tract, impaired intestinal barrier function and immune responses, and dysregulation of the intestinal microbiota are involved in the pathogenesis of CD. Deterioration of intraepithelial lymphocytes function, such as overactivity of cytotoxic T lymphocytes or a decrease in their anti-inflammatory activity, may contribute to CD [8].

Diagnosis and treatment

There is no definitive diagnostic research for CD. The combination of endoscopy, radiology and histological criteria is used for diagnosis [9]. Since it is usually diagnosed during adolescence, growth retardation is the most important complication for the pediatric patient group [10]. One of the biggest challenges associated with CD is that 80% of patients need a diagnosis after 20 years of illness, and about 30% require surgery within 5 years after diagnosis [6]. In cases of colonic or ileal Crohn, endoscopic findings are classically characterized by varying degrees of skipping lesions, as well as areas of mucous that appear to be normal [6]. Ileocolonoscopy examination and biopsy have been determined as the first-line investigation for suspected CD. This diagnostic method is superior in diagnosing mild ileal CD. However, intubation of the terminal ileum may not always be possible, and up to 20% of patients have isolated proximal small bowel disease beyond the reach of complete ileocolonoscopy [11]. Magnetic resonance imaging with ileocolonoscopy exami-

nation and Computed Tomography (CT) are complementary in the diagnosis of ileal CD [11].

Symptoms can vary depending on the location and severity of the disease. Symptoms include diarrhea and abdominal pain, fatigue, weight loss, fever, anemia, and recurrent fistulas or other perianal signs (ulcers or cracks)[8].

Therapeutic agents

There are many different drugs used in the treatment of CD. The choice of medication depends on the severity of the disease and response to previous treatments. Corticosteroids are the most commonly used drugs to treat CD [4]. The main role of antibiotics is to treat the complications of CD. Immunosuppressants have been used to treat CD for many years. However, they are typically used to maintain remission due to the slow onset of action. Anti-TNF agents have been the mainstay of CD treatment. More recently approved drugs are monoclonal antibodies to certain integrins (α4 or α4β7) or interleukins (IL-12 / IL-23) [6].

Crohn disease and COVID-19

Patients with Inflammatory Bowel Disease (IBD) may be at severe risk of COVID-19 due to immunosuppressant medications or a chronic inflammatory disease state. The risks and benefits of treatment with corticosteroids should be considered, especially if individuals with IBD require new treatment / treatments because of an exacerbation or incipient disease [12]. Older age among patients with IBD, increased number of comorbidities and systemic corticosteroid use are strong risk factors for adverse COVID-19 outcomes. It is recommended to reduce corticosteroid exposure whenever possible [12,13,14]. Surgical treatments other than emergency procedures should be delayed until the symptoms of COVID-19 subside [12]. According to the British Society of Gastroenterology (BSG), topical corticosteroids or individual enteral nutrition should be administered as an alternative for patients experiencing exacerbation [13]. Both BSG and the European Crohn's and Colitis Organization (ECCO) recommend caution when initiating combination therapy [13]. Regarding the use of corticosteroids in the case of Crohn's patients with COVID-19 infection, The British Society of Gastroenterology recommends "special enteral nutrition", European Crohn's and Colitis Organization, "careful consideration if its use is to be continued", International Organization for the Study of Inflammatory Bowel Disease, "stop (reduce it appropriately) and not stop using topical steroids." [13].

It has been found that IBD patients have a higher risk of developing SARS-CoV-2 infection than healthy individuals [15]. As of May 2020, 1302 COVID-19 cases with IBD have been recorded from 46 countries. Of these, 30% were hospitalized, 6% remained in intensive care, 5% needed mechanical ventilation, and 3% passed away. According to these data, the need for mechanical ventilation and mortality due to COVID-19 is not increased among individuals with IBD [12]. Data on the outcome of the effects of SARS-CoV-2 infection in IBD patients are insufficient [15]. All individuals with IBD should take the necessary precautions to avoid COVID-19 transmission in general, including the use of masks, hand washing, social distancing and avoiding face-to-face visits [12].

Nutrition treatment in Crohn disease

CD is a chronic, recurrent and inflammatory disease. It is especially associated with 20-85% malnutrition [16]. Malnutrition

in Crohn, this may result from decreased oral intake, increased nutritional requirements and gastrointestinal nutrient losses, and sometimes drug-nutrient interactions [17]. Inadequate oral intake causes hypercatabolism due to inflammation in the acute period or malabsorption after surgical intervention and side effects arising from different treatment strategies [16]. Since CD is a life-long disease, the aim of treatment is to create remission in the short term and maintain remission in the long term with the complementary use of pharmacological, nutritional and surgical treatments [1,18]. Nutritional support is important in treating patients with weight loss or malnutrition, as the role of diet in the development of CD remains unclear [4,6]. Approximately 75% of hospitalized CD patients are reported to have malnutrition and 33% have a BMI <20 kg / m². Nutritional deficiency screening is required in patients with chronic diseases [17]. In addition, factors such as disease location, disease activity and severity, previous response to treatment and the presence of complications affect the choice of medical treatment [1].

Energy balance

Overall, the energy requirements of patients with IBD are similar to those of the healthy population [19]. One study measured total energy expenditure in adults with CD, and resting energy expenditure per kilogram in adult patients was the same or higher than that measured in healthy controls. However, this may be caused by insufficient attention to body size or tissues with different metabolic activities. A consistent relationship between CD activity and resting energy expenditure in adults has not been shown. In children with CD, measured resting energy expenditure has not been shown to be significantly different [19].

Intake of macronutrients

There was no association between carbohydrate intake and CD risk. A prospective study found no association between total carbohydrate, sugar, and starch intake and CD risk (Goens, 2020). An important component of the Western diet thought to play a role in CD risk is animal protein. In one study supporting this hypothesis, a prospective cohort of women aged 40-65 was used and was associated with an increased risk of IBD, especially in those with higher intake of animal protein from meat or fish. In subsequent studies, it has not been shown that there is a relationship between dietary protein and the risk of CD [20]. Protein requirement should be increased according to the recommended intake in active IBD and general population (1.2-1.5 g/kg/day in adults). There is no good evidence that IBD patients in remission differ from their daily protein needs from healthy controls. The protein requirement in remission does not usually increase and should be similar to what is recommended for the healthy population (about 1 g/kg/day in adults). [19]. Corticosteroids increase protein loss in children and adults with CH. In contrast, the administration of elemental or polymeric feeding as a treatment or supplemental nutritional supplement results in decreased proteolysis and lean tissue removal in children and adults [19].

The calorie-adjusted intake of total fat, saturated fats, mono and polyunsaturated fats were not found to be associated with CD risk [19]. Dietary fat was thought to play a role in the development of CD, as previous epidemiological studies found a relationship between total fat intake, saturated fat, and n-6 polyunsaturated fat and the incidence of CD. However, cohort studies have not found an association of fat intake with CD risk [20].

Intake of micronutrients

IBD patients should be checked regularly for micronutrient deficiencies and specific deficiencies should be treated appropriately. Deficiencies of various micronutrients were detected in patients in remission. Daily multivitamin supplements can correct most deficiencies, but are not guaranteed long-term efficacy. Individuals may require specific replacement therapy for iron, zinc, and vitamin D [19]. The consequences of impaired micronutrient status include anemia, impaired linear growth, and poor bone health. According to recent studies, it has been emphasized that vitamin D and its receptor may have some immunomodulatory properties in patients with IBD [19].

Consumption of dietary fiber

Depending on the ratios of soluble and insoluble carbohydrate components, dietary fibers may have varying physiological effects on the gut microbiome, gut transit time and barrier function, and nutrient absorption. In the studies reported so far, fiber obtained from fruit sources showed a decrease in CD risk compared to fiber obtained from cereals, whole grains or legumes [20]. In addition, they found that more fiber intake during adolescence was associated with a lower risk of CD. Comparing women with low dietary fiber to women who received an average of 24 grams of dietary fiber per day, a significant reduction in CD risk was seen [19].

Complementary and alternative therapies

Medicines used in the treatment of Crohn's Disease are expensive and have side effects. Due to the anti-inflammatory and antioxidant effects of curcumin, it has been used in the therapeutic approach of IBD in some clinical studies and promising results have been obtained. It is difficult to evaluate the results of the use of curcumin formulations in CD patients as they vary in terms of treatment time and route of administration [21]. Since curcumin is inexpensive to use, effective and has no side effects, it can reduce the inflammatory process in IBD treatment [22].

According to the study conducted on Crohn's patients, the administration of nutritional supplements that increase the EPA, DHA, omega-3 index and vitamin D serum levels has shown a significant effect [23]. Omega-3 reduces the concentration of arachidonic acid, the essential substrate of enzymes that produce pro-inflammatory cytokines. Omega-3 fatty acids may be beneficial in maintaining remission of Crohn's disease. However, there is no recommendation about omega-3 dosages in the guidelines yet [24]. On the other hand, although there are some studies showing that probiotics are beneficial for other gastrointestinal system diseases such as irritable bowel syndrome and ulcerative colitis, their efficacy in CD remains unclear [25, 26]. While probiotics are significantly effective in ulcerative colitis, more studies are needed to determine whether probiotics have an effect on CD [27,28].

Nutrition recommendations in active disease and remission periods

There is no generally recommended "IBD diet" to increase remission in IBD patients during active disease periods [19]. Special enteral nutrition is recommended as the first line of treatment to achieve remission in children and adolescents with acute active CD [29]. In pediatrics, special enteral nutrition is considered the primary treatment option to induce disease remission [30,4,11]. It not only improves nutritional status, but

also positively affects the growth of children [11]. In a study, it was concluded that although special enteral nutrition is an effective method in the treatment of CD, patients do not want to use this treatment due to the lack of communication between the patient and the doctor and its cost [31]. In a meta-analysis study, showed that specific enteral nutrition is as effective as corticosteroids in inducing remission in 73% of pediatric patients, but there is insufficient evidence in adults [4, 11]. Although corticosteroids have been found to be more effective in inducing remission in adults to achieve remission, low mucosal healing rates, steroid dependence, increased risk of infection, and other side effects limit the use of corticosteroids [18, 32, 33]. It found that while only 40% of American pediatric gastroenterologists thought it was a suitable or extremely suitable method for inducing remission in children with CD, 80% of patients believed diet was important.

Various studies show that steroids are superior to special enteral nutrition in adult patients, but the reason for this are unknown [18]. Although studies on adults are insufficient, there is evidence that special enteral nutrition, if tolerated, can alter the microbiome and be effective in inducing remission even in the presence of complications [11,32]. In a study conducted in adults, it was found that there was no difference between EEN and corticosteroids in inducing CD remission, and the obstacle in treatment with special enteral nutrition was nutritional compliance. Forty one percent of the patients discontinued special enteral nutrition therapy due to the deterioration of their normal life and their unpleasant taste [34]. In studies conducted with individuals with active CD, inflammatory responses have been found to reduce plasma micronutrient concentrations by lowering serum albumin apart from body stores. In addition, low levels of micronutrients such as folic acid, vitamin B₁₂, vitamin C, vitamin D, zinc, and selenium have been reported [35]. In patients with active disease who are treated with steroids (adults and children), serum calcium and vitamin 25 (OH) D should be monitored and supplemented if necessary to prevent low bone mineral density. Assessment of vitamin D deficiency in IBD, and especially in IBD patients treated with steroids, it is always recommended to provide sufficient calcium and vitamin D. Limiting corticosteroid use helps prevent low bone mineral density [19]. As the primary therapy, enteral nutrition provides all of the daily nutritional requirements through orally administered liquid formulations or through nasogastric or gastrostomy tubes for a period of 6-8 weeks [18]. Nutritional deficiencies in patients with Crohn's disease result from systemic inflammation, decreased oral intake, malabsorption and drug-related side effects due to active disease. For CDs who are malnourished or at risk of malnutrition, oral nutritional supplements can be well tolerated. If daily nutritional requirements cannot be adequately met by oral intake, alternative routes such as enteral nutrition can be used in patients to achieve targeting [16]. Generally, there is no need to follow a specific diet during remission stages. In CD, enteral nutrition is the first treatment method to provide remission with the nutrition of the patient. Parenteral nutrition, another nutritional method, can be applied to patients with CD with preoperative environment or with intestinal failure. When compared to enteral nutrition, it does not provide an additional advantage to the patient over enteral nutrition [16]. Since lactase deficiency is common in those with CD, a lactose-limited diet is required. What should be given in control, lactose and lactose-containing foods, spices, frying, gas-causing and pulp-rich foods are not given in the diet because they are not well tolerated, helping to prolong the remission period [19].

Special enteral nutrition is a diet therapy used in the treatment of pediatric CD. Thus, steroid exposure in pediatric patients is limited, it improves the nutritional status and positively affects the growth of children. In the adult population, the use of enteral nutrition therapy is low, with factors such as patient preference and biological therapy and increasing therapeutic options that affect its use. More studies are needed to evaluate the effectiveness of special enteral nutrition in adults. Evidence regarding the diagnosis and treatment of CD remains limited. Each patient should be evaluated individually to determine which study is the most appropriate, taking into account factors such as disease location, disease severity, age. Individuals with CD are not at higher risk of contracting COVID-19 infection than healthy individuals. However, in case of infection, special enteral nutrition is recommended instead of corticosteroids. If corticosteroids are to be used, they should be used carefully.

As a result, nutrient deficiencies should be replaced since the risk of malnutrition occurs in the active period of the disease. During acute exacerbations, a nutrition program prepared specifically for the patient. In the active period, the amount of protein given in the diet should be increased due to inflammation. Since lactase enzyme deficiency may occur, the administration of milk and dairy products containing lactose should be restricted as it may cause digestive disturbances. If there is not enough energy and protein intake with oral nutrition, enteral or parenteral nutrition should be done. In the remission period, when sufficient energy and protein requirements are provided, a normal diet should be started.

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