The role of diet in inflammatory bowel diseases

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2. Associate Professor Marin Tota, MD, PhD

3. Full Professor Vlatka Sotošek, MD, PhD

The graduation thesis contains 26 pages, 5 figures, 21 references.

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List of abbreviations and acronyms

BMI – Body mass index

CD – Crohn's disease

CRP – C-reactive protein

ECCO – European Crohn's and Colitis Organization

EEN – Exclusive enteral nutrition

EIM – Extraintestinal manifestations

EPIC – European Prospective Investigation in Cancer and Nutrition

ESPEN – European Society for Clinical Nutrition and Metabolism

FODMAP – Fermentable, Oligosaccharides, Disaccharides, Monosaccharides and Polyols

GBF – Germinated barley foodstuff

GLIM – Global Leadership Initiative on Malnutrition

IBD – Inflammatory bowel disease

IBD-NST – IBD-Specific Nutrition Self-Screening Tool

IC – Indeterminate colitis

IL – Interleukin

LFD – Low-FODMAP diet

MRI – Magnet resonance imaging

NHS – Nurses' Health Study

NOD2 – Nucleotide oligomerization domain containing the protein 2

NSAID – Nonsteroidal anti-inflammatory drug

PEN – Partial enteral nutrition

PSC – Primary sclerosing cholangitis

PUFAs – Polyunsaturated fatty acids

RCT – Randomized controlled trials

SaskIBD-NR Tool – Saskatchewan Inflammatory Bowel Disease-Nutrition Risk Tool

SFA – Saturated fatty acids

TNF – Tumor necrosis factor

UC – Ulcerative colitis

1. Introduction

The term inflammatory bowel disease (IBD) covers mainly the two diseases ulcerative colitis (UC) and Crohn's disease (CD) which both have similar characteristics and symptoms related to the gastrointestinal tract. Some of them include diarrhea, abdominal pain, rectal bleeding and loss of weight. Differences may be observed at the location they occur. While CD may affect all parts of the digestive tract reaching from mouth to anus and additionally penetrate all layers of the intestine, UC just affects the mucosal layer of the colon. Symptoms of both may range from mild to severe and in some cases even life threatening. Due to the immune stimulation, additional symptoms such as pain and fever may accompany the disease process. Most patients get their diagnosis at an early age and are in need of medical guidance and closer monitoring due to the higher risk of potential complications. Even though the incidence rises worldwide the precise etiology of these diseases remains largely unknown, yet a series of genetic and environmental factors can be attributed to piled incidences of IBDs. One of these environmental factors which is associated with the onset and course of IBDs is diet and thus, the nutritional components. Suspicion arises that the Western diet, which is high in fats and sugar and simultaneously low in fruits and vegetables, may significantly contribute to increased incidences of IBDs. Additionally, it is proven that Western diet lowers the diversity of the gut microbiome. (1–3)

Since diet acts on the composition of the gut microbiota, it reciprocally acts on the intestinal homeostasis. However, inflammation of parts of the intestinal tract can also induce dysbiosis and may have a negative effect on the uptake and utilization of nutrients from foods by host cells as well as the gut microbiota. The microbes use the nutrients supplied by food intake for their growth and their colonization, while host cells utilize microbial metabolites for energy provision and immunomodulation which in turn can control and maintain the intestinal homeostasis. (4)

2. Aims and objectives

This review paper puts the aspect of nutrition into the context of etiology, course, and management of inflammatory bowel diseases. For a broad overview, it illustrates the basics of clinical picture, diagnoses, and treatment options for these diseases. Furthermore, it outlines the interaction between different diets and the gastrointestinal tract, which is the main organ involved in the pathology of inflammatory bowel diseases. Highlighted are also the assessment and evaluation of malnutrition and nutrients impacted most often by it. The paper points out benefits and disadvantages of using certain nutrients to regulate inflammatory processes with the aim to induce or retain remission in patients. The goal is to provide a condensed yet comprehensive overview of nutrition in the modern context of inflammatory bowel diseases with current recommendations and treatment options.

3. Literature review

3.1 Inflammatory bowel diseases

In the category of IBD, mainly two diseases are classified, CD and UC. Both are similar in the sense that they affect the digestive tract and cause similar symptoms. Although the main etiology of these diseases remains unclear untill this day, several risk factors in the genetic and environmental field may contribute to the increasing incidence, not just in the developed countries, but also in the developing world. Incidences of both diseases are encountered predominantly in urban areas compared to rural areas with an early onset mostly in the ages of 15-29 years. (1,5)

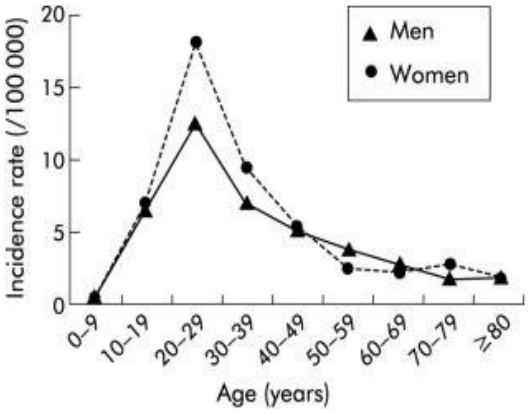

Figure1: Incidence of CD in northern France by age and gender (5)

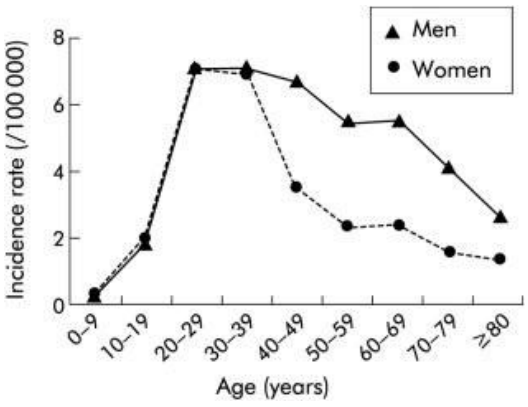

Figure2: Incidence of UC in northern France by age and gender (5)

However, there is a third type of IBD called indeterminate colitis (IC). Originally it was used for 10-15% of cases which could not clearly be categorized as CD or UC in the specimen of colectomy. Nowadays, IC is referred to as an IBD which cannot be definitively classified as CD or UC due to colonoscopy, biopsies or after colectomy. An IBD which has features of both combined is the classic example for the term of IC. The reason for the variation of reported cases of IC in the world may be explained precisely by diagnostic difficulties and differences of diagnostic possibility in different regions of the world. It can be said that the definition of IC

is not made purely by histology from one specimen, but rather a combination of clinical picture and pathology. (6)

Finally, digestive disorders are mediated by inflammation of the digestive tract and may impact the quality of life significantly. In the following sections the two main diseases CD and UC are illuminated in more detail, focusing on their characteristics, symptoms, diagnosis, and treatment options.

3.1.1 Epidemiology and etiology

Over the last decades, the epidemiology of IBD has undergone considerable changes. Especially in the developing world the incidences of IBDs are peaking but also in the developed countries the incidences rise among the population. Previously they were considered to be diseases of children and young adults but lately there is a rise in incidences also in older people and even elderly. (7)

To this date the etiology is not yet completely understood but studies support the assumption that multiple factors form the field of genetics, environment, and microbiology contribute to the etiopathogenesis of IBD. In 2001, a correlation between the occurrence of CD and a mutation in the nucleotide oligomerization domain containing the protein 2 (NOD2) gene was found. This gene is important for the function of a certain protein that acts as a receptor to recognize pathogenic bacteria by their bacterial building wall. Additionally, NOD2 is induced in tumor necrosis factor (TNF) alpha stimulated cells in the intestinal epithelium through and NF-KB- dependent mechanism so that their response to Lipopolysaccharides is increased, which in turn is critical for eradication of certain pathogenic bacteria such as Salmonella typhimurium. With this in mind, genetic testing may be a viable choice to assess at least this risk factor to develop an IBD. (8,9)

Although the interplay between all the etiological factors is not fully disclosed yet, it is certain that they influence each other and that they lead to inflammation. A central etiological role has the microbiome. In individuals with IBD it is different than in people who are not affected by these diseases. However, it is not clear whether the inflammation in the intestine causes the change of the composition, resulting in dysbiosis of the microbiome or the altered microbiome causes the inflammation in the intestine. IBD patients express a decline in microbiota species. In comparison with healthy people, they often reveal an increased number of Bacteroidete and Proteobacteria, like Enterobacteriaceae such as Escherichia coli. Simultaneously they demonstrate a smaller number of Firmicutes like Lactobacillus. In short, IBD patients have less bacteria which produce butyrate, a fatty acid that positively regulates the balance of the intestine and thus, reduces inflammation. The microbiome exerts influence upon certain genes and their activation, causing the expression of genes which may contribute to the development of IBDs. (8)

With innovative technologies and techniques observing geographical data it became possible in recent years to analyze environmental factors in better detail. In a study from Ontario, exposure

to air pollution in form of reactive oxygen species in early life was linked to an increased risk of IBD development in later years. On the other hand, being surrounded by nature with a lot of green space and blue space like water bodies in childhood turned out to be a protective factor against IBD. These environmental mechanisms are yet to be illuminated but they might act through improvement of immune tolerance, decreased levels of stress, healthier diet, more physical activity, and less exposure to pollutants. Lifestyle changes caused by urbanization have significant impact on the onset of IBDs. From birth, the immune system must adapt to the outer world. The first step of modulation of the immune system and the establishment of microbiome in newborns are largely impacted by breastfeeding. In several epidemiological studies, breastfeeding was depicted as a protective factor in the context of IBDs. Later in life, extremely processed food consumption correlates with a higher prevalence of IBDs according to Nurses' Health Study (NHS). Substances contained in such processed foods are synthetic emulsifiers which disrupt the mucosal barrier according to a pilot clinical trial, and food coloring substances, especially these for red and yellow colors are a contributing factor for intestinal inflammation in mice models. Contrary to that, mediterranean diet with healthful foods rich in fruits, vegetables, seafood and nuts, demonstrated itself as a protective factor against CD. Smoking increases the risk of CD development and additionally enhances disease progression while simultaneously diminishing the response to biologics in the therapy. For UC the data are not that straight forward. In the field of health-related etiology, infections count as a risk factor, particularly gastrointestinal infections with bacteria like Salmonella and Campylobacter. The sometimes-inevitable use of antibiotics comes also along with the other risk factors for IBD development. Starting from pregnancy the repetitive use of antibiotics may account for a higher risk for IBD. A cohort study mentions that three or more cycles of antibiotic use during pregnancy enhances the risk for UC development in the unborn child by 45%. Even in elderly people the risk is increased by the use of antibiotics. Broad-spectrum antibiotics seem to play a more significant role as a risk factor than narrow-spectrum antibiotics. The explanation for this may be that the microbiome equilibrium gets disturbed which also was mentioned as a risk factor. Last but not least, appendicitis and concomitant appendectomy have been set into the context of IBD risk. A Swedish cohort study revealed that an early appendectomy at the age of 20 or earlier lowers the risk for UC. Furthermore, appendicitis and appendectomy may change the course of UC if already present. These results are clearly laid out and summarized in figure 3. (7)

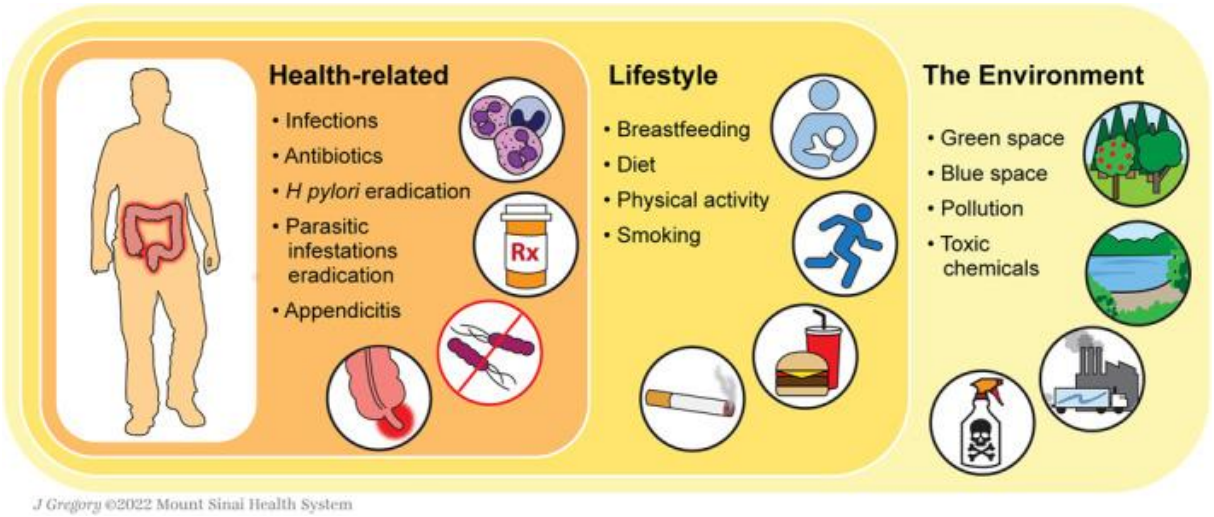

Figure 3: Factors associated with development of IBD (7)

3.1.2 Pathophysiology

The pathophysiology of both IBDs is built on environmental factors and genetic predisposition. However, studies on twins pose that genetic predisposition plays a greater role in the pathophysiological process in genesis of CD compared to UC. Most of the risk genes affect the symbiosis between microbes and the bowel. The major environmental factor for CD is cigarette smoking, even though consumption of antibiotics during childhood and adolescence also plays a central role. Additionally, dysbiosis of the microflora is observed especially in the terminal ileum and colon which hosts the highest concentration of bacteria in the gastrointestinal tract. Simultaneously direct contact of bacteria and the mucosal epithelium is noted in IBD patients compared to healthy individuals which makes IBDs not just classic autoimmune disorders but more complex barrier disorders. (10)

3.1.3 Symptoms and diagnosis

The symptoms of IBDs can vary widely among individuals, type of the disease, location of the inflammation in the gastrointestinal tract and the severity. Understanding and spotting these nuanced manifestations is crucial to make an exact diagnosis and intervene timely.

One of the most prevalent symptoms in both diseases is chronic diarrhea, which often is bloody in UC. It is marked by loose stools with increased frequency. As differential diagnosis, certain questions should be asked about in the anamnesis. Intolerance to food, intake of certain drugs, especially nonsteroidal anti-inflammatory drugs (NSAID), recent travel and cigarette smoking are crucial to ask for. (10) Other typical symptoms include weakness, fatigue, abdominal pain, weight variations and rectal bleeding. In children a growth disorder can be observed. (1)

Extraintestinal manifestations (EIM) of IBDs contribute to morbidity significantly, sometimes they may even outweigh the disease itself. Patients affected by them range from 5-50%. The most common EIM can be found in the musculoskeletal system where it manifests as spondyloarthritis, dactylitis, enthesitis or sacroiliitis. Most common representatives for the cutaneous manifestations are erythema nodosum, sweet syndrome, pyoderma gangrenosum, and oral aphthous lesions. The third most common EIMs are linked to the eyes and include conditions like episcleritis, scleritis, and uveitis. Manifestations of hepatobiliary origin are reported in approximately 50% of patients in the course of their disease and include fatty liver disease, primary sclerosing cholangitis (PSC), cholestasis, autoimmune/granulomatous hepatitis, autoimmune pancreatitis and gallstone formation. (11)

Besides taking a thorough anamnesis and asking the patient detailed questions about his or her symptoms, it is important that the patient undergoes a complete physical examination to make the right diagnosis and also to distinguish CD from UC. CD patients typically will appear underweight compared to most of UC patients. An increased heart rate combined with patients complains of fatigue and weakness may indicate acute anemia. Palpation and auscultation of the abdomen will often reveal pathologic bowel sounds, a mass in the abdomen and pain during palpation. Patients complaining about pain in the right lower quadrant are likely to have an involvement of the ileum in CD. On the other hand, left lower quadrant pain in UC patients is caused by inflammation of the sigmoid colon. The anal region should be inspected in search of a perianal fistula, a fissure or abscess in CD. Additionally, a rectal examination can provide

information about sphincter function, coarse rectal mucosa abnormalities, and hematochezia. To check for EIM, the skin and oral mucosa are examined.

Further help in the diagnosis of IBDs can be provided by laboratory tests of the blood and stool. Even though no specific blood tests are available to diagnose IBDs, some abnormalities of certain values in the blood can raise suspicion. An elevation of leukocytes and the thrombocyte count as well as the increase of acute phase reactants like the C-reactive protein (CRP) point to a state of active intestinal inflammation. In chronic inflammation, anemia often may prevail, with its degree related to the inflammation load in CD. That makes the hematocrit and hemoglobin values particularly important in the diagnostic assessment. Furthermore, the function of the liver can be checked with the parameters of cholestasis like bilirubin, alkaline phosphatase, and gamma-glutamyl transferase. Decreased albumin and serum protein levels in general point towards severe loss of proteins or malabsorption. Stool examination provides important information about pathogenic bacteria, viruses, parasites and Clostridium difficile toxins and aids in making the differential diagnosis of infectious colitis. (12)

Endoscopy evaluation plays a pivotal role for the diagnostic approach of IBDs and their therapeutic monitoring. The immense benefits of it are the precise high-definition imaging, which enables a diagnosis accurately in a little bit less than 9 out of 10 cases. In addition to the endoscopic inspection of the intestine, sampling of suspicious tissue supporting pathological reports is a major benefit and is the most accurate way to underline the suspicion of an IBD. (13) In suspicion of CD, the terminal ileum must be visualized since most mucosal changes will appear there. In UC on the other hand, it is often enough to perform a sigmoidoscopy because maximal inflammation will be nearly always in the rectum. Also, the upper gastrointestinal tract should be evaluated in the initial diagnosis by esophagogastroduodenoscopy with concomitant biopsy because extensive involvement within CD patients is accompanied by a worse prognosis. Other diagnostic tools include ultrasonography and magnetic resonance enterography of the small intestine. Magnetic resonance imaging (MRI) can help in the evaluation of stenoses and assess the wall thickening and perfusion to differentiate fibrotic from inflammatory stenoses. For the purpose of excluding a toxic megacolon a plane abdominal x-ray may be enough. (10)

3.1.4 Differences between Crohn's disease and Ulcerative colitis

Differentiating between the two subtypes of IBD is not always easy and close attention has to be given to make an accurate diagnosis. In this section, the main differences between them will be put in contrast.

In UC the inflammation usually begins in the rectum and spreads continuously and uninterrupted up the colon. Features of this inflammation of the mucosa are fluid shifting which leads to edema, ulcers which may or may not bleed and electrolyte deficits. In 20% of patients, disease is strictly confined to the rectum, while in 15% of patients have pancolitis which means that the whole bowel is affected by the diseases. In a chronic course of the disease the colon loses its flexibility and becomes shorter, more rigid and loses its characteristic haustra in the affected area. CD on the other hand can affect arbitrary parts of the gastrointestinal tract and it is marked by its characteristic skip lesions, meaning the inflammation is not continuous as seen in UC patients. Besides inflammation, strictures and development of fistulas are features of CD. However, the key feature which distinguishes it from UC is its transmural pathology meaning that all layers of the colon are affected compared to UC that solely affects the mucosa. The linear ulcers between the normal mucosa will force the mucosa to have a cobblestone appearance. Most commonly affected by are the ileum and the colon with typical exempt of the rectum. Even though in CD the esophagus, stomach or duodenum can be affected, only 5% do have an involvement of these parts. In children who firstly develop CD the incidence of upper tract involvement is higher. (14)

Symptomatically, both diseases cause diarrhea and abdominal pain, located more in the right lower quadrant in CD and in the left lower quadrant in UC. This is due to the fact that the ileum lies in the right lower quadrant while the sigmoid is located in the left lower quadrant. Malnutrition is frequent in CD also due to the location of the disease because the small bowel is responsible for the absorption of nutrients. In UC malnutrition arises occasionally. Obstructive symptoms are also solely attributed to CD and not to UC. In the laboratory, anemia, increased reactant proteins (like CRP) and hypoalbuminemia are seen frequently in CD, while they occur just in severe presentation of UC. Extraintestinal manifestations and complications like erythema nodosum, arthralgia, arthritis and ileus are more commonly seen in CD while UC has a higher number of primary sclerosing cholangitis, hepatitis and toxic megacolon. (12)

3.1.5 Treatment and Management

Since IBDs are autoimmune diseases, there is no cure for them. The aim of treatment is to induce remission of the disease. Treatment is carried out by a stepwise approach proportional to the severity of the disease. In UC the severity is graded by the extent of the disease and presence of extraintestinal manifestations. In CD on the other hand, the fraction of the gastrointestinal tract involved is significant. Stages are classified from mild to moderate to severe. Pharmacologically the first step in the management of IBDs are aminosalicylates like mesalamine. In case this therapy alone does not show sufficient improvement, the next step is to complement it with corticosteroids. In mild cases for example, oral budesonide is added because the general side-effects of corticosteroids are limited this way. In more extensive cases systemic therapy with prednisolone might be indicated. The third step is the inclusion of immune-modifying drugs like azathioprine, methotrexate, or anti-TNF. They are used if steroids are required for a long time, cannot be reduced without reoccurrence of symptoms, or the patient remains unresponsive to them. The final step is to add clinical trial agents which are particularly disease specific. For CD these are thalidomide and interleukin (IL)-11 and for UC nicotine patch, heparin and butyrate enema are used. (14)

3.2 Diet in the etiology of inflammatory bowel diseases

While several genetic and environmental factors are involved in the etiology of IBDs, the correlation between nutritional factors and the risk of developing an IBD has been researched in certain epidemiological studies. Early retrospective case-control studies display westernized diet, which is high in meat, sugar and fat, and especially polyunsaturated fatty acids (PUFAs) which have a central role in the regulation of immunological and inflammatory response, and concomitantly provides a lower supply of vegetables, fruits and fibers, as a risk factor in the pathogenesis of IBD. Large prospective cohort studies were carried out, for instance by the European Prospective Investigation in Cancer and Nutrition (EPIC) or the NHS. (4) The EPIC studies suggest that an increased consumption of docohexaenoic acid correlates with a reduced risk of developing CD. (15) On the other hand, the NHS study indicates that a high fiber intake, especially these derived from fruits, lowers the risk of CD but had no impact on UC. (16)

Figure 4 summarizes the outcome of several epidemiological, clinical and animal studies and demonstrates the positive, as well as the negative effects of certain dietary factors on IBDs. A beneficial impact is provided by diet high in fiber, fruits, vegetables, fish, amino acids, omega-3 PUFAs and vitamin D. They promote multiplication of beneficial bacteria and reciprocally decrease the number of opportunistic pathogens which in turn provide a positive impact on the total intestinal microbiota. At the level of the epithelial barrier they stimulate the mucus secretion, improve the defense mechanism of tight junctions and boost antimicrobial molecules. Lastly, they lower the presence of T helper cells (Th1 and Th2), increase the number of T regulatory cells (Treg) and also increase anti-inflammatory cytokines which has an anti-inflammatory impact on the mucosal immunity and provides protection and better regulation of the mucosal immunity. Contrary, red and processed meat, food additives, sugar, trans fatty acids, saturated fatty acids (SFA) and omega-6 PUFAs tend to have a negative impact on the microbiota in the gut, mucosal immunity and epithelial barrier. (4)

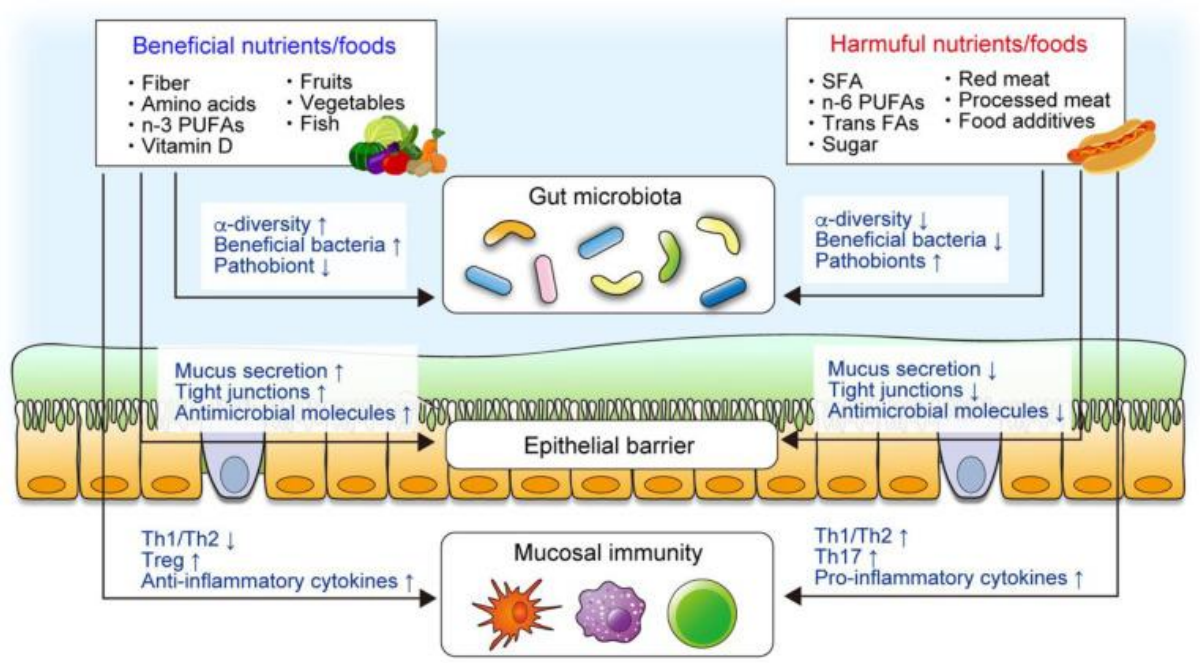

Figure 4: Influence of dietary factors on gut microbiota, epithelial barrier, and mucosal immunity (4)

3.2.1 Nutritional impact on the course of disease

As already mentioned, diet and nutrients can play a central role in the etiopathogenesis of IBDs, but it also may affect exacerbation and remission periods. Hereinafter, the exclusionary diet options and their effect on the course of IBDs will be discussed.

A diet which is often encountered in literature when researching food in IBDs is the low-FODMAP diet (LFD). FODMAPs (Fermentable, Oligosaccharides, Disaccharides, Monosaccharides and Polyols) classify a type of nutrients which are poorly absorbed in the small intestine and therefore will be fermented in the colon by the resident microorganisms. Because of this and because FODMAPs are osmotic molecules, they can trigger IBD-like symptoms such as bloating, abdominal pain and diarrhea or constipation in people who are prone to it. In a retrospective study from 2009 with 72 IBD patients, there was a significant improvement in 56% of participants who report so have less or ameliorated abdominal symptoms like pain, bloating and diarrhea leading to an improved quality of life. (17)

More generalized recommendations are grouped by the fact if currently there is an exacerbation of the disease or if the patient is situated in a period of remission. During the exacerbation period recommendations strictly advise a low fiber intake, especially if symptoms like diarrhea or abdominal pain prevail. Anyway, there is an exception to this rule which applies to UC patients with have UC with pure rectal involvement or who are prone to develop constipation. These patients are advised by the World Gastroenterology Organization to stay on a fiber rich diet. For pediatric patients the European Crohn's and Colitis Organization (ECCO) recommends staying on a normal diet during exacerbation periods.

For diet in the phase of remission the recommendations are not very clear and undisputed. According to a survey study two out of three IBD patients report avoiding certain foods to circumvent exacerbation of their disease. The fact that there are no clear recommendations underlies the theme that various authors of research papers present contradictory results. However, some recommendations presented from various publications will be shown in the following.

Some authors discovered a negative impact of sulfur products on the course of UC because sulfur affects colonocytes negatively due to the fact that the intestinal concentration of hydrogen sulfide rises. Groceries which contain bigger sources of sulfur are these with a high protein content because of the sulfur containing amino acids. These are for example cheese,

eggs, nuts and red meat. Inorganic sulfur compounds can be found in cruciferous vegetables and preserved food products. Germinated barley foodstuff (GBF) terms a prebiotic product containing glutamine-rich protein and fiber. They may improve recovery and function of colonocytes and were given to patients with mild or moderate UC exacerbations with 20-30 g of GBF daily. Four weeks later, patients reported symptomatic improvement and even endoscopic proof of betterment was noticed. With the property of achieving a prolonged remission and improved clinical picture, giving prebiotics like GBF may become a possible treatment option in future therapy implementation. However, these results still require confirmation in a larger study. Other studies highlighted a negative effect of alcohol in patients in current remission of their IBDs. Consumption led to exacerbation of symptoms and moreover an increased risk of exacerbation in progression of UC. (18)

3.3 Nutritional assessment

Due to the common interference of inflammation in individuals affected by IBDs with their digestion, they tend to have a lack in essential nutrients and micronutrients. For this reason, a proper nutritional assessment should be taken repeatedly. Important information to look after is the body mass index (BMI) and recent weight loss in the anamnesis of the patient. Other crucial factors to include in the assessment are the nitrogen balance and protein breakdown. Biochemical parameters like albumin, prealbumin, cholesterol, glucose, portal vein insulin/glucagon ratio and ferritin are as well important. Similarly crucial is the evaluation of hematologic or immunologic parameters as the total lymphocyte count and the CRP.

Following current recommendations, dominant markers of severe malnutrition are loss of weight by more than 10-15% within a period of six months, a BMI below 18,5 kg/m² and serum albumin levels lower than 30 g/L. A two-step assessment of malnutrition was suggested by the Global Leadership Initiative on Malnutrition (GLIM) in 2016. While the first step uses various screening tools to identify individuals who are “at risk” to develop malnutrition, the second step evaluates the extent of malnutrition. The criteria determined for these steps are: three phenotypic criteria (unintentional weight loss, reduction of muscle mass, and low BMI) and two etiologic criteria (reduction of food intake and inflammation or disease burden). As stated by GLIM, for the diagnosis of malnutrition at least one of each, the phenotypic and the etiologic criteria, has to be fulfilled.

There are nutritional scores which are intentionally created to perform nutritional screening in people suffering from IBD. One of these is the Saskatchewan Inflammatory Bowel Disease-Nutrition Risk Tool (SaskIBD-NR Tool). When creating this screening score, the authors had five key criteria: simplicity and quickness, non-invasiveness and economy, validity and reliability, easiness completing and finally, used data should be routinely available. It reflects gastrointestinal signs, loss of weight, anorexia and restriction of food. Questions asked to evaluate these components closer are inquired in each of these categories. For the gastrointestinal signs SaskIBD-NR Tool asks about symptoms of diarrhea, nausea and vomiting. Moreover, intake of nutrients, intake of food and avoidance of food, as well as unintended loss of weight. These questions give more information about the activity of the disease. Weight loss evaluation can shed light on the protein-energy malnutrition status and restriction of food may reveal micronutrient deficiencies. However, the SaskIBD-NR Tool aims

to detect early signs and risk of malnutrition and patients who are already malnourished are not advised to use this tool.

Another tool specific to IBD patients is the IBD Specific Nutrition Self-Screening Tool (IBD-NST) which is used for outpatients. The IBD-specific objective and subjective parameters of nutritional status utilized in this tool provide a more accurate prediction of nutritional risk compared to other tools designed merely for general malnutrition screening. This tool incorporates factors such as BMI, weight loss, clinical signs of IBD, and nutritional concerns to effectively evaluate a patient's current status and initiate necessary nutritional support.

To sum up this section, the nutritional assessment of IBD patients involves the use of both general nutritional screening tools and IBD-specific tools. Whichever tool or combination of them is used, the purpose of them is to detect risk of malnutrition as early as possible to make the decision of intervention fast and effectively combat malnutrition and its morbid effects. (19)

3.4 Malnutrition in inflammatory bowel disease

3.4.1 Mechanisms of malnutrition

Malnutrition is not attributed to only one single factor but has more of a multifactorial origin. Clearly reduction of food intake orally is one of the main reasons for malnutrition in patients affected by IBD. The reason comes down to the symptoms which accompany these diseases like nausea, vomiting, abdominal pain, diarrhea and even loss of appetite but they may also be triggered by medications taken to fight these diseases. Glucocorticoids for example often reduce phosphorus, zinc, and calcium absorption, thus leading to osteoporosis. Long-term sulfasalazine therapy may be a cause of anemia because it is a folic acid antagonist. Food intake reduction is often seen in hospitalized patients because hospitalization prolongs the period of restrictive diet or reduces the food intake in general. An additional mechanism of malnutrition is malabsorption, attributable to mucosal alterations such as damaged epithelial integrity and thus impaired transepithelial transport. Largely this is seen in CD patients in whom the ileum is affected leading to a great reduction of nutrient absorption. Especially, ionic transport is known to cause loss of electrolytes and fluids. Furthermore, inflammation may cause local chronic bleeding with connected protein loss within the intestinal system. One cause of inflammation is the overgrowth of bacteria, especially in the small intestine which may also lead to nutrient loss by increasing the permeability and therefore decrease absorption time of the intestine and production of osmotically active metabolites which induces diarrhea. A consequence of these mechanisms is an accelerated transit of valuable nutrients in the gastrointestinal tract, leading to a reduction in contact time that is essential for proper nutrient absorption. In patients with severe symptoms surgery may be indicated. However, there are some facts to consider in terms of malnutrition after surgery. The resection of larger segments of the bowel, particularly the small intestine, also leads inevitably to an accelerated transit time of nutrients with watery diarrhea and makes patients prone to malnutrition. Surgical resection of the ileum which exceeds 100 cm results in a loss of bile acids in a rate faster than hepatic synthesis, making it harder to digest fat and perform proper absorption, thus causing steatorrhea. These mechanisms are summed up and depicted in figure 5. (20)

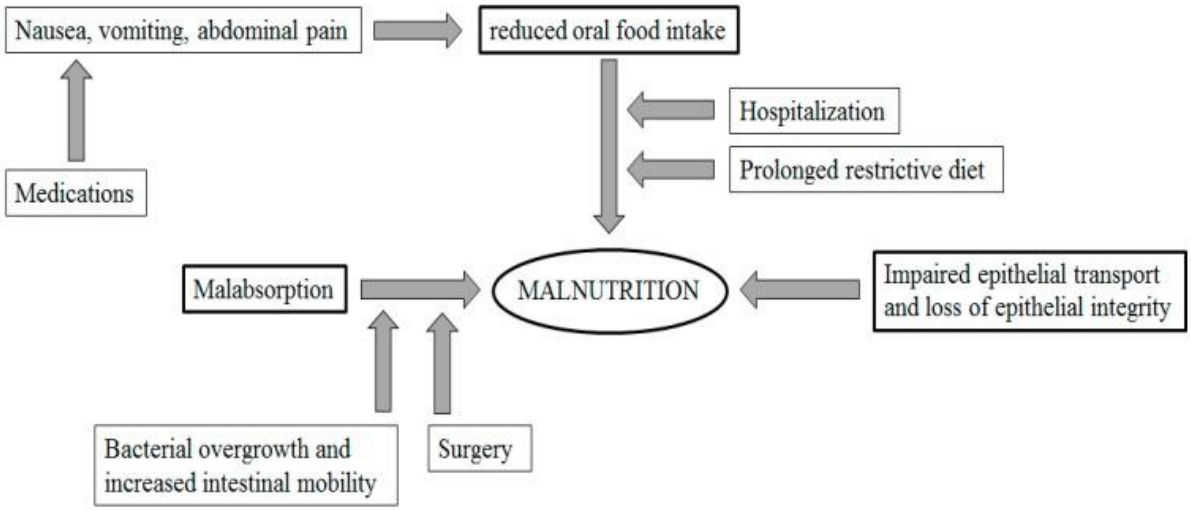

Figure 5: Mechanisms of malnutrition in patients with IBD (20)

3.4.2 Common nutrients affected by malnutrition

The British Dietetic Association advises to check serum micronutrients of IBD patients. Some of the most common nutrients that should be looked for are given below in the following.

European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines state that IBD patients have similar energy requirements as healthy people. Though, these needs may be higher in individuals with an active disease, explained by hypermetabolism and a process of acute inflammation. Therefore, protein intake in those patients should be increased to 1,2-1,5 g/kg/d in adults. In the phase of remission these increased needs do not apply anymore. However, according to ESPEN development of a deficiency of micronutrients has an even higher risk. Some of the most important will be mentioned in the following section.

Since Iron-deficiency anemia is the most frequent extraintestinal manifestation of IBDs, it is unavoidable to regularly ensure proper iron intake. Iron plays a key role in the constitution of red blood cells, making its absence cause anemia which is seen in 6-74% of IBD patients, particularly in those with CD. As soon as iron deficiency anemia is detected in IBD patients, iron should be supplemented to correct anemia.

An additional nutrient that often is deficient and should be monitored in IBD patients is vitamin D. Caution should be taken in patients with active disease who receive corticosteroid therapy. To prevent a decrease in bone density and thus osteopenia and osteoporosis with their complications, it is advised to supplement vitamin D in high-risk patients in both the active and remission phase. Furthermore, it is known that vitamin D affects the distribution of fecal microbiota in a positive way, leading to a proportional increase of beneficial microbiota and simultaneously a decrease of pathogenic microbiota. It also has the effect of protecting the intestinal barrier by regulation of thigh junction proteins and inhibition of intestinal apoptosis. A relation to disease activity was also made and supplementation can weaken the intensity of activity. IBD patients with normal vitamin D concentrations show a better outcome, lower risk of relapse and a decreased need for surgery which all together leads to an improved quality of life. (19)

Besides malnutrition of vitamin D, malnutrition of calcium is also common in IBD patients who engage into a therapy with glucocorticoids which makes them even more vulnerable to osteoporosis. Since IBD patients often stay away from milk and dairy products avoiding their lactose contents, it is important to achieve adequate calcium supply. It should be

noted that there is no proof that intolerance to lactose is more common in IBD affected people than in the healthy population.

Deficiencies of vitamin B are frequent in patients with CD, impacting 28-48% of patients in case of B12 and 4,3-54% of patients for folic acid. Cyanocobalamin, an essential compound of vitamin B12 may become deficient due to malabsorption particularly after resection of the distal part of the bowel or in severe disease involving the distal gastrointestinal tract. A lack in folic acid may prevail especially in patients under sulphasalazine therapy. Consequences of these deficiencies are macrocytic anemia and hyperhomocysteinemia. Therefore, levels should be monitored and in need of supplementation, vitamin B12 preparations should be provided parenterally. Folate deficient patients should receive supplement with folic acid if needed. (18)

For zinc, the concentration in the serum is reduced during the acute phase of IBD caused by decreased availability of albumin and chronic diarrhea leading to loss of zinc due to easy involuntary excretion. In patients with IBD the results of the zinc status are highly controversial in world literature and patients may have much the same or lower zinc concentrations than healthy individuals. In case of lower concentrations or deficiencies, supplements may be contemplated during the acute phase of IBD. Similarly, selenium displays a lower concentration in the acute phase for the same reason and levels should be corrected to ensure a proper nutritional status. (19)

In conclusion, deficiencies in vitamins and minerals are prevalent among individuals with IBDs and are optimally addressed through supplementation to achieve recommended levels. If left untreated, these deficiencies can exacerbate disease severity and lead to comorbid conditions. Nonetheless, further evidence-based strategies, supported by rigorously designed clinical trials with accurate documentation of deficiencies and supplementation levels, are necessary to evaluate the benefits of preventive supplementation.

3.5 Nutritional treatment options of inflammatory bowel diseases

The fact that diet has a huge impact on the course of IBD is supported by several studies. Various dietary elements have demonstrated the ability to either alleviate or exacerbate inflammation in IBD. Consequently, there has been considerable interest in utilizing dietary adjustments as supplementary or alternative therapeutic approaches for managing IBD. Presently, numerous nutritional strategies such as enteral nutrition and dietary modifications are being employed in IBD treatment. These interventions have exhibited efficacy in inducing clinical remission and promoting mucosal healing. Although the exact mechanisms remain incompletely understood, it is evident that nutritional interventions exert an influence on the composition of the gut microbiota, suggesting that manipulation of the gut microbiota may be one of the underlying mechanisms. (4)

3.5.1 Enteral nutrition

Exclusive enteral nutrition (EEN) is the most thoroughly researched nutritional intervention known for its efficacy in inducing remission in patients with CD. Recent meta-analyses have highlighted its superior efficacy over corticosteroids in pediatric CD patients. Furthermore, findings from open-label randomized controlled trials (RCTs) have underscored EEN's capacity to more effectively promote mucosal healing in pediatric CD compared to corticosteroids. Conversely, in adult CD patients, enteral nutrition's efficacy falls short of corticosteroids, primarily due to its poor palatability. The mechanisms underlying EEN's efficacy include bowel rest, anti-inflammatory properties, modulation of gut microbiota, and restoration of the intestinal epithelial barrier. EEN induces significant alterations in gut microbiota composition; however, the resulting microbial community differs notably from that of healthy individuals. Studies indicate that EEN treatment diminishes α-diversity and beneficial bacterial populations like Faecalibacterium and Bifidobacterium. Yet, the precise mechanisms linking these microbial alterations during EEN to the attenuation of intestinal inflammation remain unclear, warranting further investigation. A deeper understanding of these mechanisms holds promise for developing novel dietary-based therapeutic strategies for managing IBD. (4)

3.5.2 Parenteral nutrition

Partial enteral nutrition (PEN) involves the consumption of 50% to 90% of total calories from formula, supplemented with whole foods. In a study PEN was compared to EEN to assess the influence of a conventional diet on active pediatric Crohn's disease (CD). Fifty children diagnosed with active CD were randomly assigned to receive either 50% PEN or EEN. Although both groups experienced symptom alleviation and nutritional improvements, the PEN group exhibited significantly lower rates of remission compared to the EEN group (15% vs. 42%). Furthermore, the EEN group demonstrated significant enhancements in laboratory parameters such as increased albumin levels and reduced erythrocyte sedimentation rate in contrast to the PEN group. These findings underscore the impact of a standard diet on the inflammatory status in CD. (21)

4. Conclusion

In conclusion, the etiopathogenesis of IBDs remains incompletely understood, with multiple contributing factors. However, the role of nutrition is unequivocally significant. Various studies and papers present conflicting views on the optimal diet for individuals with IBD, yet they converge on the notion that a personalized approach, tailored to symptomatic progression, is essential and should be guided by professional consultation.

A diets rich in fiber, fruits, vegetables, fish, amino acids, PUFAs, and vitamin D are potentially beneficial. These dietary components may positively modulate the intestinal microbiota and enhance the epithelial barrier at the cellular level. As the focus shifts toward preventive strategies, there is a need for more comprehensive studies to harmonize findings and establish consensus dietary guidelines.

Meticulous monitoring and regulation of nutrient intake, particularly micronutrients prone to deficiency, are crucial for optimizing treatment outcomes and preventing additional morbidity associated with malnutrition.

5. Summary

The review presents a focused examination of IBDs, primarily concentrating on CD and UC, encompassing their etiology, pathophysiology, clinical manifestations, diagnostic modalities, therapeutic strategies, and nutritional considerations. Etiologically, a complex interplay of genetic predisposition and environmental triggers are accountable for the rising global incidence of IBDs. Clinical manifestations vary but common symptoms include chronic diarrhea, abdominal pain, fatigue, and weight changes. Diagnosis entails a comprehensive evaluation including detailed clinical history, physical examination, laboratory assessment, and endoscopic investigation to differentiate between CD and UC accurately. Distinguishing features between CD and UC lie in their distinct patterns of inflammation and distribution within the gastrointestinal tract. Therapeutically, management of IBDs adopts a stepwise approach aimed at inducing and maintaining disease remission while minimizing complications. Treatment modalities encompass a range of pharmacological agents, including aminosalicylates, corticosteroids, and immunomodulators, tailored according to disease severity and response to therapy. Nutritional considerations play a pivotal role in the management of IBDs, with dietary factors exerting a significant influence on disease activity and progression. While Western diets rich in meats, sugars, and fats are associated with increased IBD risk, diets abundant in fiber, fruits, vegetables, and omega-3 PUFAs confer protective effects. Furthermore, malnutrition of various origins represents a common complication in IBDs. Nutritional assessment tools, alongside regular monitoring of biochemical parameters, aid in early detection and management of malnutrition. Nutritional interventions, especially enteral nutrition, play a vital role in achieving and maintaining disease remission, particularly in pediatric CD patients.

Key words: inflammatory bowel diseases, gastrointestinal tract, diet, malnutrition, treatment

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7. Curriculum Vitae

Adrijan Kalić, born on June 3, 1994, in Stuttgart, Germany, began his educational journey in 2001 at elementary school. Following a 13-year academic path, he successfully earned his Abitur in 2014 from the Mathilde-Planck-Schule (Ernährungswissenschaftliches Gymnasium) in Ludwigsburg. In the same year he started high higher education, enrolling in the Study program of Nutrition science at the University of Hohenheim which he did not fully complete. In 2017 he enrolled into the study program of Biochemistry at the University of Tübingen for one year. In 2018 he enrolled in the English study program of Medicine at the University of Rijeka in Croatia. He is on track to complete his medical studies by the summer of 2024. Additionally, during his study time at the University of Hohenheim, Adrijan Kalić has actively engaged in coaching and teaching as academic assistant and tutor to deepen his scientific understanding.