Chapter 3

NUTRITION AND INFLAMMATORY BOWEL DISEASE

Karla Bascuñán¹², David Díaz-Jiménez¹, Rodrigo Quera³ and Marcela A. Hermoso¹,*

¹Laboratory of Innate Immunity, Institute of Biomedical Sciences (ICBM), Faculty of Medicine, Chile
²School of Nutrition and Dietetics, Faculty of Medicine, University of Chile, Chile
³Department of Gastroenterology, Clínica Las Condes, Chile

ABSTRACT

Inflammatory bowel disease (IBD) comprise a heterogeneous group of chronic diseases of unknown etiology and unclear pathogenesis. These mainly include Crohn's disease and Ulcerative Colitis. Increased disease incidence and prevalence have paralleled economic and social development. Dietary changes are possible factors to explain the development of this pathology. Diet, an environmental factor amenable to significant change, appears to be a determinant factor for IBD onset. The Westernized diet, low in dietary fiber and high in refined sugar and animal fats, has been proposed as an IBD risk factor.

Studies suggest various associations between diet and IBD development. For example, increased consumption of refined carbohydrates may modulate the onset of IBD. Also, the alteration of essential fatty acids (omega-6:omega 3 ratio) may affect their modulation of both innate and acquired immunity through the generation of eicosanoids, molecules of a lipid nature produced by the oxygenation of essential fatty acids. These molecules are generated from long-chain polyunsaturated fatty acids (LCPUFA) and represent a key link between LCPUFA and inflammation. On the other hand, the consumption of functional foods such as probiotics and prebiotics may promote an optimal intestinal environment in patients with IBD. Breast feeding has also been shown to have a protective effect.

Therefore, diet can be a protective factor against IBD and an adjunct therapy once the disease is established. This is an important factor that could improve quality of life of patients with these diseases.

* E-mail: mhermoso@med.uchile.cl.
Keywords: Diet, Inflammatory Bowel Disease, Nutrition, Inflammation, Essential fatty acids

INTRODUCTION

Inflammatory bowel disease (IBD) comprise a heterogeneous group of chronic diseases of unknown etiology and unclear pathogenesis, described as relapsing chronic inflammatory disorders of the gastrointestinal tract, including Crohn’s disease (CD) and Ulcerative Colitis (UC) [1]. In CD, the areas most affected are the ileum and colon, although compromised tissue may include any area between the mouth and anus. On the other hand, in UC, involvement is often limited to the mucosa of the rectum and colon [2]. Both diseases affect millions of individuals worldwide, affecting quality of life and causing disabling symptoms.

IBD incidence varies among populations. Rates are high in the U.S. and U.K., affecting one out of every 250 people, and lower in Asia, South America and New Zealand. IBD emerges mainly at two points in the lifespan: the first in young people 15 to 30 years old; the second in adults 60 to 80 years old. About 30% of patients are diagnosed before the age of 20 [3]. Growing IBD incidence and prevalence have paralleled worldwide economic and social development. The disease has been attributed to consequences of a Westernized lifestyle, such as smoking, oral contraceptives, non-steroidal anti-inflammatory drugs, and stress [4].

IBD are multifactorial and polygenic diseases resulting from the interaction of three co-essential factors: genetic susceptibility, immune response, and the environment. Key environmental factors include the local microenvironment (gut microbiota); bacterial infections (such as Listeria spp., E. coli and Streptococci) [5], smoking (a complex, decisive factor in IBD manifestation in predisposed individuals that, interestingly, worsens evolution of CD, but is protective in UC [6, 7]); use of oral contraceptives (with a stronger association for CD patients) [8]; and diet, which plays a critical role in IBD pathogenesis. Data suggest that nutrition is an etiologic factor for IBD, linked to new dietary habits in the population; the rise in IBD incidence in developing countries and has been proportional to the concomitant emergence of new dietary patterns [9]. This model is associated with increased consumption of cow’s milk in children, high intake of refined carbohydrates and fats, and low consumption of dietary fiber in the form of fruits and vegetables [10].

The diet is an environmental factor amenable to significant modifications and represents a key factor in IBD onset. The gastrointestinal tract is exposed to a sustained quantity and quality of food antigens and therefore, there is a close interaction between food components (nutrients) and cells present in the gastrointestinal mucosa. The interaction of fatty acids with transcriptional factors contributes to modulation of several inflammatory responses [11]. A case-control study carried out in children recently diagnosed with CD, concluded that imbalanced consumption of fatty acids, vegetables and fruits was associated with increased disease risk [12]. Furthermore, dietary factors in IBD etiology, such as consumption of sugary foods prior to IBD diagnosis, were positively associated with disease development in a case-control multicenter study [13]. Thus, an imbalanced diet in terms of food nutrient composition might be an environmental factor associated with IBD development.
ROLE OF DIET IN THE PREVENTION OF IBD

The Westernized diet, low in fiber and high in refined sugar and animal fats, has been proposed as a risk factor for IBD development [14, 15]. In Japan, an increase in CD incidence has been correlated with a Westernization of the diet [16]. Dietary constituents of interest include refined carbohydrates, vegetable oils, animal fats and dairy products [17].

Infant-feeding Practices

Several studies have shown that breast milk consumption and duration in the newborn might reduce the risk of developing UC [18] and CD [19]. In this sense, a case-control study that included 308 infants with CD showed that the infants with CD were breastfed for less than 4.6 months while the healthy control group were breastfed for an average of 5.8 months [20].

Furthermore, the use of cow's milk early in life might be involved in IBD etiology. IBD patients have high levels of antibodies against cow's milk proteins as compared with healthy individuals [21]. A study carried out in children investigated the relationship between hypersensitivity to cow's milk during infancy and subsequent development of IBD. The frequency of hypersensitivity to cow's milk protein during childhood was evaluated in 68 IBD patients and 36 healthy controls, with the finding that incidence of hypersensitivity was 20.9% in UC, significantly higher than the 8.5% for CD and 2.8% among control infants [22]. In addition, in patients who had a previous history of reaction to cow's milk and later developed UC, age of disease onset was significantly earlier (6.68 vs. 10.62 years) than for those who did not have a history of hypersensitivity [22]. These data suggest a likely relationship between hypersensitivity to cow's milk and the subsequent development of IBD at an early age.

The relationship between breastfeeding and IBD could be explained by protective mechanisms of breast milk that help prevent gastrointestinal infections [23], stimulation of the gastrointestinal mucosa [24], immunoglobulin content, and delayed contact with cow's milk or infectious agents.

The mucosal epithelium comprises an area at least 200 times larger than the skin. This extensive and vulnerable epithelial barrier is protected by numerous mechanisms of innate immunity closely associated with adaptive immune response. This first line of defense is also made up of by antibodies as part of the humoral immunity arm, such as secretory immunoglobulin A (IgA) and immunoglobulin M (IgM) [25]. The secretion of antibodies inhibits mucosal colonization by various pathogens, and therefore, penetration by harmful soluble antigens. Interestingly, harmless proteins and some components of commensal bacteria not only stimulate the secretion of antibodies, but also activate suppressive mechanisms collectively called "oral tolerance" [26]. This mucosal-induced hyporeactivity probably explains why most individuals do not show adverse immune reactions to persistent contact with harmless environmental or dietary proteins [27].

The success of interactions between innate and adaptive immunity is a prerequisite for human health, due to the fact that the mucosa provide multiple entry portals for a vast diversity of pathogens, allergens and carcinogens. The neonatal period is particularly critical
because the newborn is immediately exposed to a large number of microorganisms, foreign proteins and chemicals. Breastfeeding is therefore very important, not only as a natural replacement therapy or passive vaccine, but also because human milk may impact greatly on immune system development [28].

The role of breastfeeding in delaying development of UC and CD may be related to three main aspects. First, there is evidence that human milk protects against some immunologically mediated diseases, such as bronchial asthma [29], atopic dermatitis [30], allergic rhinitis [31] and type 1-diabetes mellitus [32]. This effect is attributed to the immunomodulatory properties of the breast milk. Therefore, the hypothesis that human milk has an immunomodulating effect that provides protection against these diseases could be extended to prevention of UC and CD development. Second, breastfeeding during immune development is important for ensuring oral tolerance to the microbiota and dietary antigens, two factors that might contribute IBD pathogenesis [33]. Finally, human breast milk has been shown to limit colitis development in IL-10 deficient mice [34]. This finding was explained by a change in the intestinal flora from pathogenic bacteria to non-adherent bacteria, derived from oligosaccharides present in human milk that stimulate the growth of *Bifidobacterium* and *Lactobacillus* [34]. A change in the pattern of proinflammatory cytokines is another possible explanation [35].

The major evidence related to the benefits of human milk is derived from epidemiological studies carried out with UC and CD patients [18, 19]. However, great controversy remains in the literature, as others studies have failed to achieve significant results or found no association between breastfeeding and IBD development.

### Refined Carbohydrates

Refined carbohydrates, also known as simple sugars, include disaccharides (mainly lactose, fructose, galactose). Refined carbohydrates are molecular constituents of a great variety of foods, such as dairy products, fruit and table sugar. This last food is characterized by rapid intestinal absorption and a subsequent increase in plasma insulin levels. During the last decades, new dietary habits (mostly in Western populations) have included elevated consumption of refined sugars and carbohydrates, a phenomenon involved in the increasing rates of obesity and insulin resistance [36].

Since the 1970s, several studies have documented high consumption of this type of food in IBD patients. As a result, numerous authors have suggested that refined carbohydrates might increase the risk of IBD development, and in fact, consumption of refined carbohydrates is now considered a risk factor for CD and UC [37, 38]. Another study, which evaluated the pre-disease diet of 30 recently diagnosed CD patients as compared with 30 control subjects (matched for gender, age, social class and marital status), concluded that CD patients consumed considerably more refined sugars, slightly less dietary fiber and substantially less fruit and raw vegetables that the controls [39]. A diet with these characteristics is likely to precede and contribute to triggering CD development [40]. Nonetheless, the role of simple sugar consumption in IBD etiology has remained unclear, due in part to methodological limitations of some studies, in particular the retrospective nature measuring of food intake prior to IBD development [41].
**Essential Fatty Acids**

Long-chain polyunsaturated fatty acids (LCPUFA) are divided into two main groups, the ω-3 and ω-6 fatty acids. Within the ω-3 fatty acid family, α-linolenic acid (LNA, C18:3 Δ 9, 12, 15; ω-3) is the most representative and is the metabolic precursor of LCPUFA (fatty acids with ≥20 carbon atoms), such as eicosapentanoic acid (EPA, C20:5 Δ 5, 8, 11, 14, 17; ω-3) and docosahexaenoic acid (DHA, C22:6 Δ 4, 7, 10, 13, 16, 19; ω-3). In the ω-6 fatty acid family, linoleic acid (C18:2 Δ 9:12; ω-6) is the most representative and is the metabolic precursor of arachidonic acid (AA, C20:4 Δ 5, 8, 11, 14; ω-6) and docosapentanoic (DPA, C22:5 Δ 4, 7, 10, 13, 16; ω-6) fatty acids [42].

Both LNA and linoleic fatty acids are considered essential fatty acids (EFA), due to the lack of enzymes for their biosynthesis in mammals (which cannot incorporate double carbon-carbon bonds in their chains). Therefore, those fatty acids must be supplied by the diet. A high concentration of linoleic acid is found in most vegetable oils (sunflower, soybean, corn, between others). LNA is mainly found in certain seeds such as canola, soybean and chia [43]; its main metabolites, EPA and DHA, are found largely in seafood (fatty fishes and algae) (See Table 1) [43, 44].

**Lipid Mediators**

Fatty acid intake affects the lipid composition of cell membranes, especially phospholipids in neural membranes, erythrocytes, and immune system cells [45]. Membrane phospholipids of immune cells have a high content of AA, the main precursor for eicosanoids, which are produced in high quantities as a result of cellular stimulation. Eicosanoids are generated from the oxygenation of EFA, and several functions have been attributed to them, including that of a mediator of central nervous system functions, inflammation and immune response. These molecules are generated from LCPUFA of 20 carbons and represent the key association of fatty acids with inflammation. Inflammatory cells usually contain a high levels of n-6 AA and low levels of other LCPUFA, such as EPA. Moreover, large number of cytokines, such as TNFα, IL1, IL6 and IL8, and proinflammatory eicosanoids, produced through the metabolism of AA (from membrane phospholipids), have an important role in the initial phase of the inflammatory activation [46, 47].

AA can be converted to 2-series prostaglandins (PG), such as prostacyclins I2, prostaglandin E2, prostaglandin F2α, and thromboxanes (TX), leukotrienes (LT)-4, and a series of hydroperoxides and derivatives of hydroxy-eicosanoic and lypoxins. On the other hand, EPA can be converted to the PG and TX series-3, LT series-5 and various hydroxyperoxides and hydroxyl-eicosanoids derived and resolvins [48].

Of all eicosanoids produced, those synthesized from AA (e.g.: prostaglandin series-2 (PGE2) and leukotriene B4 (LTB4)) predominate in cell membranes. Studies have described that incorporation of high amounts of EPA and DHA in cell membranes results in a decreased production of eicosanoids derived from AA. This is mainly a consequence of a decrease in the amount of AA available as a substrate and particularly by the inhibition of AA metabolism [49]. In addition to these data, studies in weanling rats have shown a direct relationship between AA content in phospholipids of immune cells with the ability of these cells to produce PGE2, demonstrating that prostaglandin production increases with a diet rich in AA and diminishes in animals that receive a diet rich in EPA and DHA [50].
Table 1. Dietary sources of long n-3 PUFA

<table>
<thead>
<tr>
<th>Common Dietary Sources</th>
<th>EPA, mg/100 g</th>
<th>DHA, mg/100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anchovy</td>
<td>763</td>
<td>1,292</td>
</tr>
<tr>
<td>Herring, Atlantic</td>
<td>909</td>
<td>1,105</td>
</tr>
<tr>
<td>Salmon, farmed</td>
<td>862</td>
<td>1,104</td>
</tr>
<tr>
<td>Salmon, wild</td>
<td>411</td>
<td>1,429</td>
</tr>
<tr>
<td>Mackerel, Atlantic</td>
<td>504</td>
<td>699</td>
</tr>
<tr>
<td>Bluefish</td>
<td>323</td>
<td>665</td>
</tr>
<tr>
<td>Sardines, Atlantic</td>
<td>473</td>
<td>509</td>
</tr>
<tr>
<td>Trout</td>
<td>259</td>
<td>677</td>
</tr>
<tr>
<td>Golden bass (tilefish)</td>
<td>172</td>
<td>733</td>
</tr>
<tr>
<td>Swordfish</td>
<td>127</td>
<td>772</td>
</tr>
<tr>
<td>Tuna, white (albacore)</td>
<td>233</td>
<td>629</td>
</tr>
<tr>
<td>Mussels</td>
<td>276</td>
<td>506</td>
</tr>
<tr>
<td>Striped bass</td>
<td>169</td>
<td>585</td>
</tr>
<tr>
<td>Shark</td>
<td>258</td>
<td>431</td>
</tr>
<tr>
<td>Pollock, Atlantic</td>
<td>91</td>
<td>451</td>
</tr>
<tr>
<td>Oysters, wild</td>
<td>274</td>
<td>210</td>
</tr>
<tr>
<td>King Mackerel</td>
<td>174</td>
<td>227</td>
</tr>
<tr>
<td>Tuna, light (skipjack)</td>
<td>91</td>
<td>237</td>
</tr>
<tr>
<td>Snapper</td>
<td>48</td>
<td>273</td>
</tr>
<tr>
<td>Flounder and sole</td>
<td>168</td>
<td>132</td>
</tr>
<tr>
<td>Clams</td>
<td>138</td>
<td>146</td>
</tr>
<tr>
<td>Grouper</td>
<td>35</td>
<td>213</td>
</tr>
<tr>
<td>Halibut</td>
<td>80</td>
<td>155</td>
</tr>
<tr>
<td>Lobster</td>
<td>117</td>
<td>78</td>
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<tr>
<td>Scallops</td>
<td>72</td>
<td>104</td>
</tr>
<tr>
<td>Blue Crab</td>
<td>101</td>
<td>67</td>
</tr>
<tr>
<td>Cod, Pacific</td>
<td>42</td>
<td>118</td>
</tr>
<tr>
<td>Shrimp</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Catfish, farmed</td>
<td>20</td>
<td>69</td>
</tr>
<tr>
<td>Eggs</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>Chicken breast</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Beef</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pork</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common Dietary Sources</th>
<th>ALA, g/100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chia</td>
<td>63</td>
</tr>
<tr>
<td>Flaxseed (linseed) oil</td>
<td>53.3</td>
</tr>
<tr>
<td>Chia seed</td>
<td>17</td>
</tr>
<tr>
<td>Canola (rapeseed oil)</td>
<td>9.1</td>
</tr>
<tr>
<td>Walnuts, English</td>
<td>9.1</td>
</tr>
<tr>
<td>Butternuts</td>
<td>8.7</td>
</tr>
<tr>
<td>Soybean oil, nonhydrogenated</td>
<td>6.8</td>
</tr>
<tr>
<td>Mustard oil</td>
<td>5.9</td>
</tr>
<tr>
<td>Soybean oil, hydrogenated</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Modified with permission from Mozaffarian et al. [92]. Data are from the U.S. Department of Agriculture National Nutrition Database for Standard Reference Release 23, 2010.

ALA: alpha-linolenic acid; DHA: docosahexanoic acid; EPA: eicosapentanoic acid; PUFA: polyunsaturated fatty acid.
A beneficial effect of LCPUFA (particularly ω-3) has been found in a variety of inflammatory diseases, in humans and animal models [51]. LCPUFA are involved in the modulation of multiple processes, including innate immunity and acquired pathological infections due to bacteria and the course of chronic diseases, such as IBD; therefore, it is postulated that they could have a positive effect in patients with CD or UC [52].

The inflammatory response is part of a normal innate immune reaction when it occurs as a controlled process, including the steps of induction, regulation and resolution of inflammation [53]. It has been demonstrated that LCPUFA ω-3 have an anti-inflammatory effect, competing against the incorporation of AA within membrane phospholipids, replacing them and blocking the production of pro-inflammatory eicosanoids, especially PG2 and LT4 [53, 54].

**Signal Transduction Pathways Activated by Omega 3**

The family of peroxisome proliferator receptors (PPAR) constitutes a group of transcription factors activated by ligand that heterodimerize with the retinoic acid X receptor (RXR). PPARs recognize response elements in the promoter region of several genes, subsequently affecting gene transcription. PPARs bind several ligands, including non-steroidal anti-inflammatory drugs, thiazolidinediones, and LCPUFA and their metabolites [55]. Various receptor subtypes have been identified (α,δ,γ) and are expressed differently in different tissues. In particular, PPARγ is expressed in the intestine, primarily in the colon [56]. PPARγ has been implicated in the regulation of inflammation and has become a therapeutic target in the treatment of inflammatory disorders, including IBD. In line with this observation, PPAR ligands attenuated the expression of proinflammatory genes by NF-κB inhibition through a mechanism independent of IκB in a colonic cancer cell line [57].

The Westernized diet, rich in ω-6 fatty acids, promotes a pro-inflammatory environment which fosters the rise of pathologies of immunological as well as metabolic origin. It is important to highlight the relevant potential use of LCPUFA ω-3 supplementation in inflammatory pathologies.

**Fiber**

Fiber is the non-digestible dietary component of plants fit to be eaten, and includes lignin and polysaccharides other than starch. From a physiological point of view, fiber can be divided into two categories: fermentable (pectins, beta-glycans, gums, inulin, oligosaccharides and dextrin) and non-fermentable (cellulose, hemicellulose, lignin, waxes and resistant starch) [58].

Fermentable fiber or prebiotics have been defined as non-digestible food ingredients that beneficially affect the host by stimulating the growth and/or activity of one or a limited number of colonic commensal bacteria, contributing to colonic health [59]. Sources of dietary prebiotics include compounds such as inulin that are found in a variety of plants such as chicory, garlic, onion, banana, oatmeal, and wheat. Daily inulin intake in adults is estimated between 3-11 g/day in Europe and between 1-4 g/day in North America [60]. Oligosaccharides, another prebiotic compound, are mainly present in human milk [61] with concentrations of about 12 g/day, representing one of the most abundant components. The presence of oligosaccharides in human milk suggests that they might play an important role in the complex relationships among the gut, microbiota and immune system [62].
Prebiotics are metabolized by the gastrointestinal bacteria to produce lactate, gas, and short-chain fatty acids, such as acetate, propionate and butyrate. Among short-chain fatty acids, butyrate has an anti-inflammatory effect, promoting inhibition of the translocation to NF-κB and preventing the transcription of pro-inflammatory cytokines [63]. Butyrate also reduces colonic permeability by increasing the activation of PPAR-γ [64], an important effect as increased permeability might genetically predispose the host to developing IBD. In patients with UC in remission who were asked to eat 60 grams of oat bran per day (corresponding to 20g of dietary fiber) for 3 months, the increased production of butyrate was found to be safe and effective at increasing the levels of fecal butyrate, as a consequence of the substantial increase in dietary fiber [65].

**Probiotics**

The definition of probiotics has evolved with increased knowledge in this area. Fuller and colleagues proposed that probiotics are a dietary supplement with living microbial content that positively affects the host, improving its balance of intestinal microbes [66]. According to the World Health Organization (WHO), probiotics are live microorganisms which, when consumed in adequate amounts as part of the diet, confer a benefit to host health [67].

The human gut contains a dense, dynamic and diverse bacterial ecosystem, with important functions for health. The resident flora of the human intestine have been estimated at 500 to 1,000 different species of bacteria, with an number of total bacteria about $10^{14}$. These bacteria contain 100 times the number of genes as the human genome [68]. Microbiota composition is influenced by the age of the host, environmental factors, genetics, diet, and exposure to chemotherapy drugs and probiotics. In addition, antibiotic treatment may substantially alter the microbiota with evident effects in the long term [69].

In individuals genetically susceptible to IBD, the balance between intestinal bacteria in the intestinal mucosa might be altered, contributing to the inflammatory process. The fecal microbiota in IBD patients is quite different than that of healthy individuals [70]; there is a reduction in microbiota biodiversity with an increase in the number of bacteria that adhere to the mucosa, such as *Listeria monocytogenes*, *Escherichia coli* adherent and invasive *Mycobacterium avium paratuberculosis* (MAP)) [71-73].

There is indirect evidence supporting the hypothesis that the intestinal microbiota is important in IBD pathogenesis. For example, it has been demonstrated that there is no development of intestinal inflammation in animal models kept in a germ-free environment [74]. Moreover, experimental colitis can be successfully treated with antibacterial agents. Increasing evidence suggests that gut bacteria play a pathogenic role in CD, providing a rationale for the use of antibiotics in primary treatment of the disease [75]. A bypass of the intestinal content improves inflammatory disease in CD patients, with relapse after the restoration of the fecal flow [76]. There is a close interaction between the intestinal flora and host epithelial cells, which might contribute to the development of the inflammatory response [77]. Moreover, bacterial DNA may be an immunomodulatory component of a healthy intestinal flora or may lead to a persistent intestinal inflammation.

It has also been proposed that the bacterial flora associated with the mucosa play a larger role in IBD than the luminal flora [78]. The composition and activity of the intestinal microbiota in IBD patients is abnormal. In particular, patients with IBD show reduced levels of dominant members of the intestinal microbiota [73]. Furthermore, biopsies taken from CD and UC patients show a reduction in the rRNA sequence associated with *Firmicutes* and
Bacteroides, and a concomitant increase in the rRNA sequence 16S of Proteobacteria and Actinobacteria in comparison to controls. This finding indicates that the gastrointestinal tract of IBD patients has an abnormal bacterial content, characterized by a depletion of commensal bacteria, in particular the members of the cluster Firmicutes and Bacteroidetes [79].

Within the Enterobacteriaceae genus, Escherichia coli (E. coli) is the bacteria most commonly associated with IBD. In particular, E. coli belongs to the group B2+D (with an increased virulent potential) and is present in higher levels in patients compared to controls [80]. Adherent-invasive E. coli was the strain most commonly found in the ileum of CD patients, particularly associated with mucosal ileum lesions [81]. On the other hand, E. coli isolated from UC patients was less invasive as compared with specimens isolated from CD [82].

Some of the best evidence for the hypothesis that the microbiota plays a key role in IBD comes from work with animal models. Although experimental IBD models mimic human UC imprecisely and CD even more poorly, development of the disease is dependent on the presence of resident bacteria. A key finding from various animal models with genetic or induced disease is that chronic colon inflammation is initiated and maintained in the presence of the resident enteric bacteria, while the development of the disease is prevented or slowed down dramatically in a germ-free (sterile) condition [83].

As the majority of IBD susceptibility genes identified are involved in the regulation of innate or adaptive immunity and in the maintenance of the intestinal mucosal barrier, it is apparent that the microbiome, defined as the totality of microbe, their genetic elements (genomes), and environmental interactions in a particular environment, plays a critical role in the development and natural history of disease. Moreover, the role of probiotics in this complex microenvironment might affect the disease at different levels. Probiotics might have a direct effect on the immunologic reaction of the host, indirectly decreasing the immunologic reaction by improving the mucosal barrier function, diminishing the interaction with the host immune system, displacing deleterious microbes from luminal-mucosal interface, or by altering the metabolic consequences of the microbiome [84].

The use of probiotics has long been proposed as beneficial to human health, but in recent years, there has been increased interest in their use in IBD, as the role of the microbiome in its pathogenesis has become more apparent [85]. Probiotics are taken by IBD patients, sometimes on the advice of the physician, but mostly self-prescribed as a form of alternative medicine. Reasons for probiotic use include disease severity, side effects of conventional treatments, and health beliefs. Recent reports suggest an increase in the use of such components, with up to 50% of adult and pediatric IBD patients taking probiotics on a regular basis [86]. In a placebo-control trial, 20 patients with mild-to-moderate UC received 100 ml/day of fermented milk with bifidobacterium or placebo for 12 weeks as an adjuvant therapy; the results concluded that supplementation with fermented milk with bifidobacterium was safe and more effective in the management of UC than conventional treatment alone, suggesting that probiotics might have a beneficial effect in those patients [87].

**Synbiotic**

A further possibility in microflora management is the use of synbiotics, the combination of probiotics and prebiotics. A synbiotic has been defined as "a mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the GI tract, by selectively stimulating the growth and/or
activating the metabolism of one or a limited number of health-promoting bacteria, and thus improving host welfare” [59].

For humans, the paradigmatic symbiotic food is breast milk. Breast milk -the first food we receive after birth- contains lactic acid bacteria such as lactobacilli and bifidobacteria, oligosaccharides and nucleotides; these last are also considered bifidogenic factors [88]. For this reason, breastfed infants have a microbiota dominated by bifidobacteria and lactobacilli compared with formula-fed children. This finding probably explains the higher resistance of breastfed children to infections, diarrhea and allergies [89].

Symbiotics are also being incorporated into food for children and adults. Their health effects are likely greater than the effects of the probiotic and prebiotic separately, due to additive or synergistic effects [90, 91]. However, in order to clarify this point, clinical trials are needed to assess the effects of the synbiotic in comparison with the isolated probiotic and prebiotic components. To date, no studies have evaluated the use of synbiotics in IBD, although probiotics and prebiotics have shown effects separately.

**CONCLUSION**

Epidemiological studies provide evidence for the role of diet as an environmental factor in IBD. Eating habits almost certainly modulate disease risk in both healthy and susceptible populations, and dietary changes are a potential new treatment approach. Experimental studies are needed to elucidate the role of diet and specific nutrients on incidence, treatment and disease progression. Longitudinal epidemiological studies are also needed to assess the role of diet and nutrition on the population level.

**REFERENCES**


Nu

trition and Inflammatory Bowel Disease


