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Combinatorial Effects of Diet and Genetics on Inflammatory Bowel Disease Pathogenesis

Laura J. Dixon, PhD¹, Amrita Kabi, PhD¹, Kourtney P. Nickerson, PhD^{1,2}, and Christine McDonald, PhD^{1,2}

¹Department of Pathobiology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH

²Department of Molecular Medicine, Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, Cleveland, OH

Abstract

Inflammatory bowel disease (IBD) encompasses a group of disorders affecting the gastrointestinal tract characterized by acute and chronic inflammation. These are complex and multifactorial disorders that arise in part from a genetic predisposition. However, the increasing incidence of IBD in developing countries suggests that environmental factors, such as diet, are also critical components of disease susceptibility. Evidence suggests that consumption of a Western diet, enriched with saturated fat, refined carbohydrates, and food additives, is associated with increased IBD risk. Dietary components, such as omega-6 fatty acids, long chain fatty acids, protein, and digestible carbohydrates, may contribute to IBD pathogenesis through altering intestinal microbiota, increasing intestinal permeability, and promoting inflammation; whereas omega-3 fatty acids, medium chain triglycerides, and non-digestible carbohydrates improve these parameters and intestinal health. However, the limited amount of prospective studies, small sample sizes, and the heterogeneity of disease subtype result in inconsistencies between studies and difficulty in conclusively determining the specific effects of diet on intestinal homeostasis. There are no standard clinical dietary recommendations for IBD patients. However, exclusionary diet interventions have shown some efficacy in relieving symptoms or inducing remission, suggesting more research is needed to fully understand how diet influences disease behavior or combines with other IBD risk factors to promote disease. This review focuses on the associations of various dietary components and IBD risk in clinical studies and genetically susceptible IBD models.

Keywords

Crohn's disease; ulcerative colitis; diet; nutrition; genetics

Correspondence & Reprints: Christine McDonald, Department of Pathobiology, Lerner Research Institute, NC22, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, 216-445-7058, 216-636-0104 fax, mcdonac2@ccf.org.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) belong to a spectrum of disorders collectively referred to as inflammatory bowel disease (IBD) that are characterized by chronic, relapsing inflammation of the digestive tract¹. While CD and UC present with similar symptoms, the location and histologic features of each subtype are different. Disease symptoms are unpredictably exacerbated and occur intermittently, followed by variable length periods of remission. Disease onset is highest between the ages of 20–40, resulting in lifelong disease. Although the highest disease incidence is currently in Canada and Europe, incidence rates are increasing worldwide, indicating that IBD is rapidly becoming a global disease².

IBD is a complex and multifactorial disease resulting from the interplay of the genetic makeup of individual, environmental triggers, and alterations in the intestinal microbiome that combine to stimulate an aberrant immune response that drives chronic intestinal inflammation (Figure 1). Of these factors, the most is known about the genetics of IBD. Genome-wide association studies have identified over 160 loci linked to increased IBD susceptibility^{3, 4}. These loci implicate a diverse array of genes involved in IBD pathogenesis that encompass multiple physiological processes, including microbe recognition, lymphocyte activation, and intestinal epithelial defense.

Genetics alone, however, cannot explain the exponential rise in IBD incidence over the last fifty years². Epidemiological and clinical evidence suggest IBD is linked to diverse environmental factors, such as smoking, diet, drugs (non-steroidal anti-inflammatory drugs and oral contraceptives), geographical location, and social status². The changing pattern of IBD incidence across time and geography provides further evidence that environmental factors and lifestyle are major contributors to IBD pathogenesis. The increased prevalence of IBD cases observed in developing nations can be correlated with the adoption of a Western diet and lifestyle. Additionally, the contribution of environmental factors to disease onset is reiterated in studies showing that individuals emigrating from low incidence regions to countries with higher IBD prevalence are at an increased risk of developing IBD, especially their first-generation children⁵.

Multiple theories have been formulated to understand how environmental exposures trigger an abnormal inflammatory response. Among them, the most prominent one is the “hygiene hypothesis”⁶. It attributes the rising frequency of immunologic disorders to reduced exposure to a variety of enteric organisms during early childhood due to improved sanitation and hygiene, resulting in an ineffectually trained immune response. Another theory is the “cold chain hypothesis” which suggests that prolonged refrigeration of foods influences the bacterial content of food by promoting growth of psychotropic bacteria, such as *Yersinia spp* and *Listeria spp*, which have been identified in CD patients⁷. Both of these hypotheses indicate that alterations to the intestinal microbiota can enhance susceptibility to trigger aberrant immunologic responses linked to IBD pathogenesis. Other studies of IBD pathogenesis implicate decreased intestinal epithelial barrier properties to damage from non-steroidal anti-inflammatory drugs, alcohol, smoking, or bacterial toxins⁸. A growing body of

literature suggests that dietary factors also have significant impacts on both microbiome composition and epithelial barrier function.

While there is still some controversy about the exact role played by diet in IBD development, there are indications that diet may significantly modulate disease onset and activity. For example, high vegetable intake has been associated with decreased risk of UC, whereas greater intake of fiber and fruit is associated with decreased risk of CD⁹. Conversely, a “Westernized” diet rich in animal fat and protein and low in fiber has been strongly correlated with IBD⁹. Although somewhat variable, multiple epidemiological studies have also shown links between CD patients and a high intake of carbohydrates, starch, and refined sugar^{10–12}. Even with these and other dietary trends, there are no formal dietary guidelines for IBD patients. This is, in part, due to study design limitations (largely underpowered, retrospective studies) and heterogeneity in disease subtype (UC, CD) that contribute to variation in study results. This review provides an overview of the differential effects, either beneficial or detrimental, of dietary component families (fat, protein, carbohydrates, and additives) on gut homeostasis in the context of IBD. It further highlights findings that genetic susceptibility may also significantly impact the effect of dietary modulation on IBD pathogenesis. A detailed understanding of the effects of dietary components on intestinal homeostasis maintenance based on the genetic makeup of an individual may provide crucial insights that help design better therapeutic strategies to prevent both IBD onset and relapse.

Fat

One characteristic of a Western diet is the consumption of high levels of fats and there is evidence to suggest a causal relationship between increased fat intake and IBD incidence. This causal relationship was first hypothesized after observations temporally linked the introduction of margarine into the European diet around 1900 with the initial reports of granulomatous ileitis (CD) in this population¹³. Similar parallels were observed in two epidemiological studies of Japanese populations; one correlating high total dietary fat consumption with CD incidence between 1966–1985¹⁴, and the other linking increased UC incidence with significant changes in the Japanese diet after 1975 that increased the daily intake of meat and dairy products¹⁵. These findings are supported by the results of 19 case-control diet studies that found positive associations of high fat consumption in pre-illness diets to the risk of developing CD or UC⁹.

Further studies indicate that the type of fat may have a specific impact on disease pathogenesis. Dietary fat includes saturated fats, monounsaturated fats, and polyunsaturated fatty acids (PUFA; Table 1). There are two main types of essential fatty acids, ω -3 PUFA and ω -6 PUFA, which must be supplied through diet. These essential, short chain fatty acids are inflammatory modulators, as well as building blocks for longer chain fatty acids, such as arachidonic acid and eicosapentanoic acid that play essential roles in cell signaling¹⁶. A number of studies indicate that ω -3 PUFA is anti-inflammatory, whereas ω -6 PUFA is pro-inflammatory and a balanced ratio of ω -3 to ω -6 PUFA is essential for homeostasis¹⁶. Increased levels of ω -6 PUFA are found in Western diets and are correlated with a greater risk of developing IBD^{9, 14}. Animal models that increase levels of ω -3 PUFA, either

genetically (*fat-1* transgenic mice) or through dietary means, have demonstrated protective effects in chemically-induced colitis (dextran sulfate sodium; DSS) and the spontaneous ileitis SAMP1/Yit models^{17, 18}. Therefore, there has been significant interest in using dietary ω -3 PUFA supplementation as an anti-inflammatory treatment for IBD. However, several reports on ω -3 PUFA supplementation in patients demonstrate decreased inflammatory parameters, but no effect on disease activity or relapse rates^{19–22}. Additionally, results from two large clinical trials of ω -3 PUFA supplementation demonstrated mixed results for UC and concluded that supplementation was not effective in preventing CD relapse^{23, 24}. Intriguingly, a different study suggests that a more effective therapeutic approach may be to balance the ω -3 to ω -6 PUFA ratio, as IBD patients that achieved a ω -3/ ω -6 ratio of 1 maintained disease remission at a significantly higher rate²⁵.

In addition to fatty acid ratio, specific types of triglycerides in the diet may also affect IBD pathogenesis. Long-chain triglycerides (LCT) have been shown to stimulate inflammation through increasing intestinal lymphocyte proliferation and upregulation of pro-inflammatory mediator expression²⁶. These findings led to the suggestion that diets with reduced LCT levels (consisting of less than 20% of the energy content) would be therapeutically effective in inducing IBD remission²⁷. Conversely, medium chain triglycerides (MCT) are anti-inflammatory due to their ability to suppress production of the neutrophil chemoattractant, IL-8, which is found to be expressed at high levels in the mucosa of IBD patients with active disease^{28, 29}. In fact, dietary MCT supplementation reduced inflammatory responses in a murine trinitrobenzene sulfonic acid (TNBS) ileitis model³⁰. Likewise, in children with CD, injections of a formula containing MCT improved disease activity, suggesting this may be a beneficial approach for the future³¹.

One common consequence of a high fat diet (HFD) is obesity that, like IBD, is characterized by inflammation. Pro-inflammatory cytokine levels of interleukin-1 β (IL-1 β), IL-6, and TNF- α are elevated in both obesity and IBD^{32, 33}. Moreover, inflammatory mediators secreted from adipose tissue, such as the adipokines adiponectin, resistin, and leptin, are found in the serum of IBD patients^{34, 35}. However, it is important to note that in both prospective human studies and animal models, obesity was not associated with increased IBD incidence. For example, the European Prospective Investigation into Cancer and Nutrition (EPIC) study of over 300,000 participants who were followed prospectively up to 15 years for disease development concluded that obesity (as measured by body mass index) is not a risk factor for IBD incidence³⁶. Instead, other retrospective studies of IBD patients suggest links between obesity and higher clinical disease activity^{37, 38} and diminished therapeutic efficacy of biologics, such as adalimumab³⁹ and infliximab⁴⁰. Likewise, lean mice fed a HFD do not spontaneously develop intestinal inflammation. Instead, in a chronic DSS colitis model obese mice have aggravated intestinal histopathology⁴¹. These findings suggest that consumption of a HFD increases the risk of developing IBD independent of obesity, but a potential consequence of a HFD, obesity, may exacerbate IBD pathogenesis.

In agreement with the concept that IBD is a complex, multi-factorial disease, findings from mouse models indicate that consumption of a HFD is not sufficient to cause intestinal inflammation and that the combination of diet with genetic risk accelerates disease pathogenesis. In one study, colitis-prone *Mdr1a*^{-/-} (multiple drug resistance pump 1a) mice

were placed on a HFD for 12 weeks and compared to wildtype FVB mice on the same diet⁴². Both strains of mice gained weight on the HFD and developed inflammation of mesenteric fat, increased plasma leptin, and increased mesenteric lymph node inflammation. However, the HFD did not cause colitis in FVB mice, but resulted in exacerbated colitis in *Mdr1a*^{-/-} mice. Acceleration of colitis in a genetically susceptible background was also observed in *IL-10*^{-/-} mice fed a HFD enriched with saturated milk fat, but not in C57BL/6 wildtype mice⁴³. Similar findings were observed in an ileitis model that examined the effect of a HFD on disease in *TNF ARE/WT* (tumor necrosis factor AU-rich elements) mice, which develop a Crohn's-like ileitis⁴⁴. These findings indicate that high fat consumption is not sufficient for IBD development, but synergizes with other IBD risk factors to promote disease.

The mechanisms by which diets enriched with fats promote intestinal inflammation have been postulated to include both changes in the intestinal barrier and composition of the intestinal microbiota. Plasma endotoxin levels are increased in mice fed a HFD, independent of genotype or development of colitis, suggesting increased intestinal permeability⁴⁴. Similarly, healthy subjects placed on a Western diet for one month developed a 71% increase in plasma endotoxin levels, but not intestinal inflammation⁴⁵. One mechanism of increased intestinal permeability is the decrease of epithelial tight junction proteins, such as occludin. In multiple murine studies, consumption of a HFD has resulted in dramatic decreases of intestinal occludin expression^{44, 46, 47}. Excessive intake of dietary fats also alters the intestinal microbiota, which can significantly impact intestinal permeability and inflammation^{43, 46}. Antibiotic treatment of mice on a HFD reduced metabolic endotoxemia and restored intestinal expression of tight junction proteins⁴⁶. In addition, acceleration of colitis in *IL-10*^{-/-} mice on a high saturated milk fat diet was demonstrated to be caused by the expansion of a specific opportunistic pathogen (a pathobiont), similar to what has been observed in microbiome studies of IBD patients^{43, 48}. These studies highlight the influence of a HFD to promote IBD-associated changes to gut microbes and intestinal permeability.

In summary, there are a number of epidemiological and murine studies correlating a HFD with changes to the intestinal barrier and microbial populations that enhance the acceleration of IBD, independent of obesity. These studies emphasize the role of specific dietary fats on increasing intestinal inflammation and promoting disease in a genetically susceptible background. However, more evidence is needed to determine if fats with anti-inflammatory effects may be therapeutically beneficial in IBD.

Protein

Early investigations of the relationship between protein consumption and IBD hypothesized that intestinal inflammation in these patients was due to a milk protein allergy^{49, 50}. However, circulating levels of IgA or IgG antibodies in UC patients were similar to healthy controls, suggesting a non-antigenic response to proteins found in milk⁵⁰. Although somewhat variable, more recent studies link high protein consumption from a variety of sources, including red meat, cheese, milk, fish, nuts, and eggs, with altered IBD incidence^{9, 11, 12, 14}. One large, prospective study of the dietary patterns of French women ages 40–65 over two years demonstrated that increased protein intake, specifically animal

protein in the form of meat or fish, but not eggs or dairy, correlated with IBD development⁵¹. Another prospective study of UC patients in remission suggests that high consumption of red meat or protein significantly increased the risk of disease relapse⁵². The mechanisms of protein-induced changes that promote IBD remain incompletely understood. However, metabolites of protein may provide fermentation substrates for gut bacteria that could alter microbiome composition (pathobiont expansion) or short chain fatty acid production that would impact intestinal enterocyte function^{52, 53}, but more studies are needed to determine the precise mechanisms involved.

Carbohydrates

Carbohydrates may be classified by their degree of polymerization: mono- and disaccharides (i.e. simple sugars, such as glucose, fructose, sucrose), oligosaccharides (i.e. fructooligosaccharides/FOS, galactooligosaccharides/GOS), and polysaccharides (i.e. starch, cellulose, inulin; Table 2). They may also be classified by their availability for metabolism in the small intestine. Available carbohydrates (simple sugars, starch) are hydrolyzed and absorbed in the small intestine. Unavailable carbohydrates, also called resistant starches (inulin, pullan, FOS, GOS), cannot be hydrolyzed in the small intestine, but are fermented by the microbiota in the large intestine. Finally, insoluble fiber (such as cellulose or bran), pass through the digestive tract largely intact, have a laxative effect, and add bulk to intestinal contents⁵⁴.

Carbohydrates were first considered a dietary risk factor for IBD in 1977 when CD patients in the United Kingdom were found to consume more cornflakes for breakfast than healthy controls⁵⁵. Numerous studies have subsequently linked high sugar and low dietary fiber consumption as risk factors for IBD, and particularly CD^{9, 11, 12}. However, similar to what is observed with dietary fat, the type of carbohydrate consumed is important in determining a positive or negative effect on IBD pathogenesis.

One current hypothesis for the deleterious role of carbohydrates in IBD is the promotion of bacterial overgrowth in the intestine. High consumption of available carbohydrates, such as glucose, sucrose, lactose, or fructose, is postulated to overwhelm absorptive mechanisms of the intestine, resulting in increased luminal sugar concentrations that are then used as an energy source by the microbiota⁵⁶. In support of this hypothesis, IBD patients often have evidence of fructose malabsorption or lactose intolerance⁵⁷. In mouse studies, consumption of a high sugar diet was demonstrated to promote intestinal dysbiosis, the expansion of bacterial pathobionts, increased intestinal permeability and inflammation^{58, 59}. This concept has been popularized in the low FODMAP diet, which excludes fermentable oligo-, di-, and monosaccharides and polyols, as a treatment for IBD (see following section on Dietary Manipulation in IBD)^{60, 61}.

The increased risk of IBD associated with high sugar consumption is also paralleled by decreases in dietary fiber intake, suggesting a preventative role for this carbohydrate family in IBD^{8, 9, 11–13}. Dietary fibers are non-digestible carbohydrates that fall into three categories: soluble (e.g. pectin), insoluble (e.g. cellulose) and mixed (e.g. bran). It has been demonstrated that these non-digestible carbohydrates, termed prebiotics, bypass the small

intestine and are fermented by the microbiota in the colon to promote bacterial diversity, preserve mucosal barriers, and enhance the production of short chain fatty acids (SCFAs) that are beneficial for maintenance of intestinal homeostasis^{62–64}. In murine colitis models, prebiotic supplementation with dietary fibers, such as inulin, oligofructose, and resistant starch, has been demonstrated to decrease histopathology and inflammation in both genetic (*IL-10*^{-/-}, human major histocompatibility complex, class I, B27 (HLA-27) transgenic mice) and chemically-induced (DSS, TNBS) colitis models^{65–67}. Butyrate is one SCFA produced from prebiotic fermentation that plays an essential role in dampening intestinal inflammation and promoting mucosal homeostasis⁵³. Deficiencies in butyrate producing bacteria and decreased colonic expression of the butyrate transporter monocarboxylate transporter-1 have been observed in IBD patients^{68, 69}. In fact, butyrate enemas have shown some clinical benefit for UC patients⁷⁰ and dietary fiber supplementation to promote colonic butyrate production in prospective studies of UC patients are demonstrating therapeutic promise^{71, 72}. Due to the excellent safety profile of these carbohydrates and fermentation products, further investigation into the therapeutic efficacy and molecular mechanism of their effects is warranted.

Polysaccharide Additives

An aspect of the Western diet that has been under-examined is the effect of polysaccharide food additives, included in processed food items as stabilizers, thickeners, texturizers, emulsifiers, sweeteners, and coating agents, on IBD risk (Table 3). As societal and technological changes in the 20th century led to the increased production and consumption of processed food in the United States, there was a concomitant rise in IBD incidence^{2, 73}. The majority of these additives are generally recognized as safe (GRAS) by the Federal Food and Drug Association, but several recent studies suggest that these additives may induce changes in the intestinal barrier, microbiome shifts, bacterial overgrowth, and impairment of immune responses that may increase IBD susceptibility. For example, carrageenan is an algal polysaccharide produced from seaweed and is widely used as a thickener or stabilizer in many processed foods. It has also been suggested that it promotes intestinal damage because it is used to induce experimental colitis in mice and has been linked to increased colorectal tumors in rats^{74, 75}. Other additives, such as xanthan gum, maltodextrin, and carboxymethyl cellulose, are associated with bacterial overgrowth and intestinal inflammation in the young or genetically susceptible. A recent outbreak of necrotizing enterocolitis in pre-term infants has been linked to consumption of formula thickened with xanthan gum^{76, 77}. Likewise, bacterially-dependent necrotizing enterocolitis has been induced experimentally by feeding pre-term piglets formula enriched with another ubiquitous polysaccharide thickening agent, maltodextrin⁷⁸. Other studies demonstrate that consumption of the emulsifier, carboxymethyl cellulose, increases bacterial overgrowth in colitis-susceptible *IL-10*^{-/-} mice and post-weaning colibacillosis in piglets^{79, 80}. Maltodextrin was also linked more directly to CD pathogenesis in a study demonstrating that the mucosal microbiome of ileal CD patients is enriched with maltodextrin metabolizing bacteria⁸¹. Although maltodextrin has been shown to affect intestinal bacterial loads, mucosal barrier integrity, and anti-bacterial defenses in mice, it should be noted that maltodextrin did not induce spontaneous intestinal inflammation in either wildtype mice or

full term piglets^{82, 83}. These findings suggest that these dietary additives are not sufficient to cause disease alone, but may synergize with other risk factors to promote disease.

Effectiveness of Dietary Manipulation on IBD

Although there is a strong belief in patients that diet affects disease activity, currently there are no standard clinical recommendations on diet for IBD patients. Often this leads to patients empirically excluding diet components or seeking dietary advice on the internet that is often misleading, incomplete, or false. This is often done without the knowledge or direction of doctors or dietitians and can lead to dangerous nutrient deficiencies or malnutrition. More well-defined and controlled prospective studies are needed in order to provide IBD patients with dietary recommendations based on clinical evidence. However, there are promising findings with some dietary approaches in IBD whose therapeutic effectiveness is outlined below.

Enteral and Parenteral Nutritional Therapy

One of the most extensively studied method of feeding IBD patients is by a complete liquid diet directly into the gastrointestinal tract via a tube, catheter, or stoma, termed enteral nutrition (EN)⁸⁴. It may be used as a sole source of nutrition (exclusive enteral nutrition; EEN) or only to provide part of the diet (partial enteral nutrition; PEN). The diet may be comprised of one of three formulas: polymeric, which includes intact proteins, carbohydrates and fats; semi-elemental, which contains peptides, simple sugars, glucose or starch polymers, and fats (primarily as MCT); and elemental, which is comprised of partially or completely hydrolyzed nutrients. An elemental diet (ED) has a low amount of indigestible material or fibrous material, making this diet almost entirely absorbed by the small intestine, leaving a minimal amount of residue for stool. A related approach is parenteral nutrition (PN) therapy, which provides essential nutrients and calories intravenously. These diets, regardless of composition, are effective to promote intestinal “rest” in a number of pre- and post-operative conditions, as well as provide nutrition for IBD patients who are malnourished.

EN is a first line CD therapy in Europe and Japan^{85, 86}. This diet is thought to increase mucosal healing and is effective in promoting CD remission in pediatric CD cases⁸⁷. Likewise, total parenteral nutrition (TPN) can bring about remission in CD⁸⁸. Several studies and a meta-analysis indicate that, while EN promotes remission in ~60% of adult CD cases, it is not as effective as corticosteroids for CD therapy in adults, and therefore is not generally recommended as a first line therapy in this population³⁶. This is in contrast to findings with UC patients, where EN has not been proven effective⁸⁴. Studies indicate that EN or PN does not improve disease remission rates, enhance the effectiveness of steroid therapy, or favorably affect inflammation in UC patients with active disease. Therefore, this approach is not currently recommended for UC patients.

It's important to note that while there has been some success with EN and PN therapies, there are some drawbacks to this therapeutic approach. EN and PN diets are unpalatable, and may result in diarrhea, overhydration, hyperprothrominemia, hypoglycemia, skin rashes, and the risk of aspiration. Patient compliance with such a diet is difficult, resulting in incomplete

adherence and less therapeutic benefit. However, EN and PN may be particularly useful for pediatric CD patients to achieve disease remission, avoid corticosteroid use, and correct undernutrition to improve quality of life.

Low FODMAP diet

Bacterial overgrowth is postulated to be a result of carbohydrate malabsorption, which contributes to IBD pathogenesis through excessive carbohydrate fermentation in the distal small intestine and proximal colon. This concept led to the development of a diet low in fermentable oligo-, di-, and mono-saccharides and polyols (FODMAPs) to improve gastrointestinal symptoms found in both IBD and irritable bowel syndrome (IBS)⁶⁰. This diet has an elimination phase, followed by the reintroduction of FODMAPs one at a time to determine if specific sources or amounts of FODMAPs trigger symptoms. Originally found to be effective for IBS patients, the low FODMAP diet has been shown in a small retrospective study to be effective in reducing abdominal pain, bloating, flatulence, and diarrhea in both CD and UC patients who were in remission⁶¹. While larger, prospective studies are warranted, the complexity of low FODMAP food identification and preparation may result in low compliance and reduced efficacy unless significant assistance and guidance of a dietician is incorporated in these trials.

The Specific Carbohydrate Diet

Another elimination diet that appears promising for IBD patients is the Specific Carbohydrate Diet (SCD), which excludes the intake of complex carbohydrates, starches, grains, and dairy, while permitting consumption of monosaccharides found in certain fruits, homemade yogurt, and honey. This diet was developed by Drs. Sidney and Merrill Haas in 1924 for the treatment of celiac disease and was subsequently applied to UC patients⁸⁹. Similar to the low FODMAP diet, the basis for SCD is that poorly absorbed carbohydrates can cause bacterial fermentation in the small intestine and contribute to intestinal permeability⁶⁰. Although more studies are needed, promising results have been observed in two studies of pediatric CD patients. One retrospective review of CD patient charts showed that all disease symptoms were resolved within 3 months of initiating the SCD⁹⁰. More importantly, a small, prospective, pilot study of pediatric CD patients demonstrated significant improvement of both clinical scores and mucosal analyses after 12 weeks on the SCD and further benefits (including mucosal healing) to subjects that continued the diet for up to 52 weeks⁹¹. Preliminary reports suggest that one effect of the SCD is to increase bacterial diversity of the intestinal microbiome⁹². Therefore, the SCD appears to have promise as a therapeutic intervention, but larger studies are needed to confirm these initial results.

Lactose-free Diet

The prevalence of lactose intolerance in CD is increased over healthy controls and correlated with disease duration⁹³. Lactose intolerance is the reduced production of lactase, resulting in decreased digestion of lactose. One study found that lactase levels in IBD patients in remission were decreased and were correlated increased breath methane levels, indicating lactose intolerance and an expansion of methanogenic bacteria in microbiota of these patients⁹⁴. Patient demographics show that genetics may play a role in lactose intolerance.

Asians and Native Americans have the highest prevalence (greater than 90%) of lactose intolerance, modest prevalence (60–70%) in individuals of black, Jewish, Hispanic, and Southern European descent and those of Northern/Western European descent including have the lowest rates (10–15%)⁹⁵. For those individuals who are lactose intolerant, a lactose-free diet may improve symptoms of IBD; however, clinical studies to specifically test this dietary intervention in IBD patients still need to be performed.

Discussion

A challenge to understanding IBD susceptibility is the combinatorial nature of risk in these individuals, making it difficult to determine the individual contribution of each component to disease pathogenesis. An environmental factor, diet, plays a role in shaping the intestinal microbiota and in turn, how food is digested. Gut health is influenced not only by what is consumed, but where it is digested, the mechanism of breakdown, and the metabolites produced. Although complex, unraveling the effects of diet on IBD pathogenesis is essential, as this is one of the few risk factors that is completely controllable. Additionally, the results of these studies provide critical insights for patients that often become malnourished due to fear of eating foods that may exacerbate their disease symptoms.

Although more studies need to be performed, the current findings provide some insights into the role of fat, carbohydrate, protein, and dietary additives in IBD pathogenesis. One recurrent theme is that both the total consumption levels of a particular food category, as well as the type are critical to determining beneficial or detrimental effects. For example, high total fat consumption is correlated with increased IBD risk and exacerbation of disease activity^{9, 37, 38}; however diets enriched with MCT reduced inflammation in experimental colitis and may have some clinical promise for IBD patients^{30, 31}.

Another theme is that dietary components influence intestinal permeability and maintenance of a tight intestinal barrier is essential for gut homeostasis. Consumption of fiber or prebiotic starches results in the production of SCFA, such as butyrate, which improves intestinal barrier function^{62–64}. Conversely, intestinal permeability increases as a result of carbohydrate malabsorption, excessive consumption of fats, or damage from specific food additives^{44, 46, 47, 58, 79}.

Additionally, an expanding area of study is the effect of diet on the composition and function of the intestinal microbiome and gut health. The recurrent themes of diet-induced microbial dysbiosis or pathobiont expansion have been linked to intestinal inflammation in almost all of the dietary categories reviewed⁴⁸. This is of increasing importance to understand as the use microbiome-centered therapies, such as fecal microbiota transplantation, are currently being investigated for IBD treatment and diet may have significant impact on maintenance of therapeutic effect⁹⁶.

A final central concept is that diet is not sufficient to cause IBD development, but instead synergizes with other IBD risk factors, such as genetics, to promote disease. This concept is highlighted in studies of HFD and polysaccharide additives, such as maltodextrin or carboxymethyl cellulose, in which adult, healthy subjects showed pre-clinical changes in

inflammation, intestinal permeability, or bacterial defenses, but no intestinal disease^{82, 83}. Only when this dietary priming was combined with another risk factor (genetics, prematurity) did intestinal disease occur^{43, 58, 76–80}.

How genetic and dietary risk factors synergize to promote IBD is an emerging area of research that is likely to provide important therapeutic insights. IBD-associated polymorphisms have been linked to alterations in mucosal barrier function, innate bacterial killing, immune regulation, and microbiota function⁴. Dietary risk factors also influence many of these functions and may combine with genetic factors to either exaggerate a primary defect (dosage effect) or impair multiple intestinal homeostasis mechanisms (two-hit hypothesis). For example, individuals with genetic polymorphisms in *ECM1* have increased epithelial permeability⁹⁷ that could be increased further by consumption of a HFD^{44, 45}, leading to the increased presence of microbial antigens or microbes that overwhelm normal regulatory mechanisms. Alternately, diet can influence the functional properties microbes leading to increased epithelial adherence⁸¹ and invasion, that when combined with genetic defects in innate bacterial killing (*ATG16L1* or *NOD2* polymorphisms)⁹⁷, results in persistent infections that drive chronic inflammation. However, in order to study the role of diet and genetics in IBD, we need additional studies examining individual diet components in combination with different genetically susceptible backgrounds in animal models and inclusion of genetic analyses in dietary intervention studies.

Overall, these findings open up a novel therapeutic avenue to treat IBD through dietary manipulations based on the genetic makeup of an individual, which help reduce the inflammatory symptoms and intestinal damage associated with this disease. Although diet is not the only environmental factor that impacts IBD susceptibility or disease progression, it is one of the most easily defined and controlled. However, the application of systems biology that can account for multiple environmental risk factors, various ‘omics measures (genome, microbiome, metabolome, etc.), and clinical disease phenotype would greatly enhance our understanding of IBD mechanisms. In the future, these types of studies will allow for more effective, personalized therapeutic approaches for IBD patients and potentially preventive strategies for individuals at risk for IBD development.

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Figure 1. Genetics, microbes, and diet act in concert to maintain intestinal homeostasis
Components in each of these categories can affect intestinal function directly, as well as synergize with other categories to influence overall intestinal health. Alteration of any single component is not sufficient to cause IBD. However, consumption of a Western diet may act in combination with microbes and genetic susceptibility to accelerate IBD pathogenesis.

Table 1

Contribution of dietary fats to intestinal homeostasis

Dietary Fats		
Type	Inflammatory Profile	Important findings
Saturated Fats	Pro-inflammatory	High consumption alters intestinal microbiome, promotes pathobiont expansion, and increases intestinal permeability ^{42–47}
Polyunsaturated Fatty Acids (PUFA)	Anti-inflammatory (ω -3 PUFA) Pro-inflammatory (ω -6 PUFA)	A balanced ratio of ω -3: ω -6 PUFA promotes gut homeostasis, while increased ω -6 PUFA levels are associated with increased IBD risk ^{9, 14, 16, 25}
Triglycerides	Anti-inflammatory (medium chain length; MCT) Pro-inflammatory (long chain length; LCT)	MCT reduces inflammation in experimental ileitis and CD patients, while LCT promotes proliferation and inflammatory phenotype of T cells ^{26, 30, 31}

Table 2
Carbohydrate structures and contributions to intestinal homeostasis

Simple Sugars		
Carbohydrate	Structure	Important findings
Glucose	<p>A simple aldonic monosaccharide</p>	Glucose absorption in the intestine fluctuates in response to diet ⁵⁶
Fructose	<p>A simple ketonic monosaccharide</p>	IBD patients have abnormal fructose absorption, leading to gas, abdominal cramps and altered bowel habits ⁵⁷
Sucrose	<p>Disaccharide composed of glucose and fructose</p>	IBD patients consume more sucrose, inducing dysbiosis and promoting pathobiont expansion ^{9, 11, 1258}
Polysaccharides		
Cellulose	<p>Glucose polymer linked by $\beta(1,4)$ glycosidic bonds >100 units in length</p>	Cellulose fermentation promotes bacterial diversity, mucosal integrity and decreased whole intestinal transit times ⁶²⁻⁶⁴

Simple Sugars		
Carbohydrate	Structure	Important findings
Inulin	<div> </div> <p>Fructose polymers consisting of glucosyl and fructosyl moieties linked by $\beta(2,1)$ bonds</p>	Decreases intestinal lesions, inflammation, colitis symptoms, and fecal bacterial loads ⁶⁵⁻⁶⁷
Pullan	<div> </div> <p>Maltotriose polymer linked by α-1,4 or α-1,6 bonds</p>	Decreases intestinal lesions and increases the number of IFN- γ and IL-10 producing T-cells ⁶⁵

Table 3

Composition and effects of polysaccharide food additives on intestinal health

Polysaccharide Additives		
Additive	Structure	Important findings
Carrageenan	<p>Algal polysaccharide comprised of galactose units and 3,6 anhydrogalactose, both sulfated and nonsulfated, joined by alternating α-1,3 and β-1,4 glycosidic linkages</p>	Used to induce experimental colitis in mice and linked to increased colorectal tumors in rats ^{74, 75}
Carboxymethyl cellulose	<p>Cellulose derivative with carboxymethyl groups bound to hydroxyl groups of glucopyranose monomers on a cellulose backbone</p>	Causes bacterial overgrowth and intestinal inflammation in susceptible animals ⁷⁹
Maltodextrin	<p>Polymer of glucose, 2–20 units in length connected by α1,4 glycosidic bonds</p>	Linked to necrotizing enterocolitis in piglets, alteration of bacterial adhesion and persistence, and its metabolism is correlated with ileal CD ^{78, 81, 83}
Xanthan Gum	<p>Polymer of glucose, mannose and glucaronic acid produced by <i>Xanthomonas campestris</i></p>	Caused late onset necrotizing enterocolitis in pre-term infants ^{76, 77}