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Food and the Gut Microbiota in IBD: A Critical Connection

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Abstract

Purpose of Review—The inflammatory bowel diseases (IBD) are chronic inflammatory diseases of the gastrointestinal tract apparently due to an abnormal immune response to environmental factors in genetically susceptible hosts. The composition of the gut microbiome is thought to be a critical environmental factor in IBD, and recent evidence suggests a connection between diet and the intestinal bacteria. In this review, we describe the current evidence regarding the impact of diet on the gut microbiome and how this may be relevant to the pathogenesis of IBD.

Recent Findings—Novel culture-independent DNA sequencing technology has revolutionized the approach to the characterization of intestinal bacterial communities. Recent studies have demonstrated an association between the diet and the composition of the human microbiome. Because the development of a “dysbiotic” microbiome is thought to be involved in the pathogenesis of IBD, diet is being investigated as an important etiologic factor.

Summary—The recent studies highlighting the impact of diet on the gut microbiome provide a strong rationale for further investigation of the link between diet, the gut microbiome, and the development of IBD. Such studies may provide novel information about disease pathogenesis as well as identify new therapeutic alternatives for patients suffering from IBD.

Key Words/Phrases

Inflammatory bowel disease; bacteria; inflammation; microbiota; diet

Introduction

The human gut contains a vast number of microorganisms, collectively characterized as the “gut microbiome.” All three kingdoms of life, *Archaea*, *Bacteria*, and *Eukarya*, are represented in the gut microbial community. An estimated 10^{14} individual bacteria belonging to over 1000 species reside in the mammalian gut, making it the most densely

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populated microbial community on Earth¹. The collective genome of the human gut microbiome is predicted to be 100-fold greater than that of its human host².

At birth, the human gut is sterile. Colonization by bacteria occurs within the first several hours of life. During infancy, variability in the composition of the gut microbiome among individuals depends on factors such as mode of delivery and type of infant feeding³. Diversity increases rapidly in early childhood and this dynamic process leads to the development of the relatively more stable, yet highly distinct, adult gut microbiome⁴. The majority of the bacteria in the adult gut belong to one of four phyla, *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Bacteroidetes*⁵. Obligate anaerobes predominate⁶. Humans have evolved to exist with gut microbes in a symbiotic relationship. For example, the human gut provides the ideal environment for the microbiota to flourish. In return, the host is afforded a variety of physiological benefits including the fermentation of indigestible carbohydrates to produce short chain fatty acids, biotransformation of conjugated bile acids, synthesis of certain vitamins, and degradation of dietary oxalates^{6, 7}. While it is clear that gut microbes play a critical role in maintaining the health of the host, there is also abundant evidence to suggest that the intestinal bacteria may contribute to the pathogenesis of a variety of diseases, including the inflammatory bowel diseases.

Numerous factors, such as host genetics, antibiotic use, phylogeny of the host, intestinal inflammation, and diet, influence the composition of the gut microbiota. In this review, we describe the current evidence regarding the impact of diet on the gut microbiome and how this may be relevant to the pathogenesis of IBD.

The Use of DNA Sequencing Technology to Characterize the Gut Microbiome

Most bacteria in the gut are obligate anaerobes that are challenging to grow *in vitro*, making it difficult to profile the community structure of the gut microbiome using traditional bacterial culture techniques. Over the past decade, significant advances in DNA sequencing technology now permit an assessment of complex bacterial communities using culture-independent high throughput techniques such as 454 pyrosequencing. There are two primary culture-independent methods used to characterize the gut microbiota. One approach utilizes 16S small-subunit ribosomal (rRNA) gene sequences to determine the relative abundance of bacterial taxa present in a given sample. The 16S rRNA gene is highly conserved among bacteria, and the gene is useful as a phylogenetic marker because it includes a taxa-specific signature⁸. Alternatively, shotgun metagenomic sequencing can be performed, in which the DNA in a sample is sequenced in totality permitting not only an evaluation of microbial community structure but also allowing for an evaluation of the genomic representation of the community. This approach affords the ability to understand the functions encoded by the genomes of the gut microbes⁹. Techniques such as these, in combination with the development of sophisticated bioinformatic tools, have revolutionized the approach to the characterization of complex bacterial populations.

Diet as a Determinant of Gut Microbiota Composition

Colonization of the gut begins at birth and is highly dependent upon mode of delivery⁴. After the primary inoculation, infants have multiple exposures to human microbes and there is a rapid increase in diversity¹⁰. A recent examination of the gut microbiome composition of one infant followed over 2.5 years demonstrated a considerable change in the bacterial taxa present with the introduction of solid foods and a shift towards a more stable, adult-like microbiota with weaning¹⁰. Once established, the composition of the adult human microbiome appears to be relatively constant within individuals, at least in the short-term⁵.

Conversely, high levels of variability exist between individuals⁵. The driving force behind these inter-individual differences has not been elucidated; however, early environmental exposures are presumably involved. Palmer and colleagues examined the gut microbiome of 14 full-term, healthy infants and found significant variability between infants consistent with earlier studies¹¹. The exception to this was the remarkable similarity of the gut microbiota found in a pair of dizygotic twins which highlighted the potential importance of the environment¹¹.

There is a growing body of evidence demonstrating an association between diet and the gut microbiome. A recent analysis of fecal 16S rRNA sequences from 60 mammalian species indicated clustering according to diet (herbivore, carnivore, and omnivore) in addition to clustering according to host phylogeny¹². Shotgun metagenomic sequencing has also established that there has been a functional evolution of the gut microbiome in relation to the diet¹³. For example, microbial genes encoding for enzymes involved in carbohydrate and amino acid metabolism are dissimilar between herbivores and carnivores¹³. In humans, it appears that there has also been a long-term evolution of the host-gut microbiota symbiosis¹⁴. The development of agriculture and the domestication of animals have led to a broadening of the human diet which has, perhaps, altered the composition of the human gut microbiome¹⁴.

The notion that diet can influence the microbiota was strengthened by an examination of the fecal microbiota of European children compared to that of children from rural Africa¹⁵. There were similarities in the genera of bacteria present in the gut among the youngest children from both groups, which may be explained by breast-feeding. However, outside of this age group, there were considerable differences in the gut microbiota between the African children, fed a traditional diet high in fiber, and the European children, fed a modern Western diet. A recent study on the impact of diet on the microbiome in healthy human subjects demonstrated that long-term agrarian dietary patterns are associated with an enterotype dominated by *Prevotella*¹⁶, a genus also frequently observed in people from rural Africa¹⁵. A long-term diet high in animal protein and fats and low in carbohydrates, similar to a “Westernized” diet, is associated with high quantities of *Bacteroides* and low quantities of *Prevotella*¹⁶. The influence of diet on the microbiome is in an early stage of characterization and additional studies are essential to enhance our understanding of this relationship (Figure 1).

The impact of genetics is less well characterized. Investigations of the heritability of the microbiota are primarily comprised of studies in animal models, and these studies have been reviewed recently¹⁷. A limited number of human studies, in particular twin studies, have yielded inconsistent results^{18, 19}. It is logical to believe that genetics *and* the environment interact to shape the human gut microbiome. However, the current evidence on the role of genetics is relatively modest.

Host Genetics and the Gut Microbiota in the Pathogenesis of IBD

IBD, including Crohn's disease (CD) and ulcerative colitis (UC) affects approximately 1.5 million Americans and the incidence seems to be increasing worldwide²⁰. The pathogenesis of IBD is currently thought to involve an inappropriate and persistent inflammatory response to commensal gut microbiomes in genetically susceptible individuals. The notion that the gut microbiota plays a critical role in the development of IBD is supported by a multitude of animal studies showing that bacterial colonization of the gut is critical for the development of intestinal inflammation²¹ (Figure 1). Clinical observations in patients with IBD also support a role for the gut microbiota since IBD usually affects intestinal regions with the highest level of bacteria, and both fecal diversion and the use of antibiotics can be effective

in the management of Crohn's disease^{22, 23}. However, genetic evidence provides the strongest evidence for the role of microbes in IBD pathogenesis. Genome-wide association studies (GWAS) have already identified over 100 genetic risk loci, including 28 that are shared between Crohn's disease and ulcerative colitis²⁴. Although host genetics play a critical role in disease pathogenesis, concordance rates in monozygotic twins of 16% for ulcerative colitis and about 35% for Crohn's disease indicate that non-genetic factors play a substantial role in the development of IBD²⁵. Growing evidence suggests that many of the genetic risk alleles for IBD involve regulation of the epithelial barrier or innate immune responses important to protect the host from bacterial invasion while others involve pathways that regulate the adaptive immune system²⁴. Together, this constellation of genetic alterations support the notion that IBD is due to the inability of the host to protect against microbial invasion together with unrestrained immune activation. Furthermore, significant alterations in the gut microbiome have been associated with IBD²⁶ leading to the notion that an imbalance between protective vs. injurious bacteria may lead to a “dysbiotic” microbiome that may a role in disease pathogenesis (reviewed in²⁷).

Diet and the Gut Microbiome in IBD

It is reasonable to hypothesize that certain non-genetic factors associated with the development of IBD may be due, in part, to their effects on the gut microbiome. Environmental factors that may alter the composition of the gut microbiome include diet, the use of antibiotics, and geographic location. Population-based studies suggest that IBD is unevenly distributed throughout the world with the highest disease rates occurring in industrialized nations^{20, 28}. One theory, the hygiene hypothesis, suggests that humans living in more industrialized countries are exposed to fewer microbes or less complex microbial communities at an early age leading to the development of an immune system less able to “tolerate” exposure to the microbial-laden environment in later life resulting in inappropriate immune activation. Consistent with this notion is the possible role of diet in light of the differences in access to clean water and availability of food refrigeration in underdeveloped parts of the world. Alternatively, a “Westernized” diet rich in animal fat and protein while low in fiber, may alter the gut microbiome in a way that increases the risk for the development of IBD. The development of a “dysbiotic” microbiome has, indeed, been the source of speculation as an etiologic factor in disease pathogenesis²⁷. Of course, since the intestine is continually exposed to numerous antigens, a “Westernized” diet could contain food antigens that could perpetuate the development of IBD independent of the intestinal microbiota²⁹.

Regardless of the mechanism, there is reasonable data to support a role for diet in IBD pathogenesis (Figure 1). Several investigators have examined the association of dietary patterns and the incidence of IBD^{29, 30}. For example, the authors of a systematic review concluded that high dietary intake of total fats, polyunsaturated fatty acids (PUFAs), omega-6 fatty acids, and meat were associated with an increased risk of CD and UC; high fiber and fruit intakes were associated with a decreased CD risk; and high vegetable intake was associated with a decreased UC risk³⁰. These studies support a potential role for dietary patterns in the pathogenesis of IBD. Together with the recent data characterizing the impact of diet on the gut microbiome and its association with enterotypes¹⁶, it is tempting to speculate that the alteration of gut microbiota community structure through the consumption of agrarian vs. a “Westernized” diet may play a role in either reducing or increasing, respectively, the risk for the development of IBD.

Perhaps the strongest evidence for a role of intestinal contents on the course of IBD comes from two studies of patients who underwent ileocolonic resection for CD. These studies demonstrated that recurrence of inflammation after ileal resection is dependent on exposure

of the neoterminal ileum to fecal contents and occurs within 8 days of exposure^{31, 32}. However, it is not known which component of the fecal stream contributes to the inflammation. Bacteria, other microorganisms, the digested food particles, and a combination of factors have been suggested.

Because dietary antigens may act as important stimuli of the mucosal immune system, bowel rest with total parenteral nutrition (TPN) has been utilized as a therapy in certain patients with IBD³³. In the 1980's, TPN emerged as an important modality for the treatment of moderate to severe CD. In a prospective study of 30 patients with CD treated with bowel rest and TPN, 25 (83%) achieved initial remission, but relapse was common³⁴. A subsequent randomized controlled trial evaluating various nutritional interventions in CD showed that bowel rest was not a major factor in achieving remission³⁵. Despite the conflicting evidence, bowel rest with TPN may improve symptoms, at least in the short-term, in patients presenting with a severe exacerbation. It is possible that bowel rest alters the gut microbiome in a way that is therapeutic in IBD since fasting has been shown to have an effect on the gut microbiome, at least in mice³⁶.

In CD, exclusive enteral nutrition (EEN) with elemental, semi-elemental, and defined formula diets have been widely studied for induction of remission and are considered first line therapy in certain parts of the world^{37, 38}. These diets are also efficacious in maintaining remission³⁹. The most common protocol involves the administration of a defined formula at 100% of caloric needs for 4-12 weeks in order to induce remission⁴⁰. The formulas can be consumed orally or can be administered through a nasogastric (NG) or gastrostomy tube. A smaller percentage of calories, provided by the defined formula, may be required in order to *maintain* remission, allowing additional flexibility in the diet³⁹. EEN is an alternative to potent pharmacological agents and there are no serious associated side effects. In a recent, prospective, open-label trial, children with CD were randomized to receive oral corticosteroids or EEN with a polymeric formula for 10 weeks⁴¹. In the short term, EEN was as effective as corticosteroids in achieving clinical remission⁴¹. Interestingly, nutritional therapy was significantly more effective than corticosteroids in healing the mucosa, as determined by both endoscopic as well as histologic criteria⁴¹.

In contrast to CD, there are extremely limited data on the efficacy of enteral therapy in UC. A small randomized trial of patients with severe UC compared corticosteroids plus bowel rest with TPN versus corticosteroids plus usual diet and did not demonstrate superiority of bowel rest for outcomes other than stool volume⁴². A small randomized trial of patients hospitalized with severe UC did not observe differences in response rates to corticosteroid therapy with a polymeric diet versus TPN. However, the enterally fed patients had fewer nutrition related adverse effects and fewer post-operative infections⁴³. Based on these limited data, it is difficult to make firm conclusions on the role of diet as therapy for active UC.

While nutritional therapy has been shown to be efficacious in CD, the mechanism of action has not been characterized. Interestingly, there does not appear to be major differences in efficacy of EEN based on the composition of the formula. A Cochrane meta-analysis found similar efficacy of formulas with variable degree of protein hydrolysis in treating CD⁴⁴. Formulas with very low fat content and very low long chain triglyceride concentration may be slightly more effective, but this needs to be confirmed in future trials⁴⁴. Modulation of gut microbiota composition has been proposed although the current data are sparse⁴⁵. The available literature on this subject suggests that there is a profound change in the fecal microbiome following EEN therapy^{45, 46}. A study by Leach and colleagues evaluated the abundance of five key groups of bacteria in the stool from a cohort of patients with CD treated with EEN compared to a cohort of healthy patients on a regular diet⁴⁵. At baseline,

the diversity of bacteria present was similar between the two groups. At 8 week follow-up, however, the patients with CD treated with EEN had a significant decrease in bacterial diversity which was sustained for several months following therapy completion. In the healthy control cohort, the intestinal bacterial composition remained stable. Nutritional therapy highlights the importance of characterizing the interactions between diet, the gut microbiota, and the mucosal immune system (Figure 1).

There have been other diets proposed for the management of IBD. However, none have been adequately studied nor do they have a clearly understood mechanism of action. Many patients with IBD consider themselves to be intolerant to a few or several food items⁴⁷. The food sensitivities, however, seem to be variable among patients and cover a wide range of food products⁴⁸. Several small trials of restriction diets have demonstrated improved disease activity and prolonged time to relapse⁴⁹⁻⁵¹; however such extreme restriction diets are overall impractical and poorly accepted. In a recent trial by Rajendran, food specific IgG4 levels were used to select which foods to exclude rather than excluding nearly all foods and gradually adding back selected foods⁵². Eggs and beef were the most common foods with high IgG4 antibody levels and were therefore excluded by the greatest number of patients. The 29 patients on the exclusion diet experienced a significant reduction in symptoms based on a modified Crohn's Disease Activity Index and reduction in the erythrocyte sedimentation rate as compared to pretreatment levels. There was no control group in this study. In another small study (n=22), Chiba and colleagues demonstrated superiority of the semi-vegetarian diet versus an omnivorous diet to maintain clinical remission (94% vs. 33%)⁵³. This study included patients with medically or surgically induced remission of CD who received a lacto-ova-vegetarian diet in hospital. After discharge, the semi-vegetarian diet permitted the consumption of fish once weekly and meat once every two weeks. Eggs were allowed without limitation. It should be noted that this was not a randomized trial, but rather allowed patients to choose whether or not to continue on the diet after discharge. Dietary patterns may also affect the natural history of UC. Jowett et al. prospectively observed that patients who reported higher amounts of meat, eggs, protein, and alcohol consumption were more likely to experience a relapse of UC⁵⁴. The association was much stronger for red and processed meats than for other meats. As described earlier, the results of these studies are broadly consistent with previous epidemiologic associations of IBD with industrialized nations geographically and the consumption of a "Westernized" diet high in animal fat and protein. If additional studies support the use of restriction diets in the management of IBD, further investigation of its impact on the gut microbiome may provide valuable insights that may help to further refine dietary composition to maximize therapeutic efficacy as well as provide novel information about disease pathogenesis.

Conclusion

It is currently believed that IBD is the result of a defect in innate immune protection against the gut microbiota combined with an inappropriately regulated adaptive immune response. Technological advances that now permit a more comprehensive characterization of complex microbial communities, together with recent studies showing the impact of diet on the gut microbiome, provide a strong rationale for further investigation of the link between diet, the gut microbiome, and the development of IBD. The results of these studies may not only provide important insights into the increasing incidence of IBD, geographic clustering in industrialized nations, and the association with a "Westernized" diet, but may also provide mechanistic insights into currently used dietary interventions apparently efficacious in the management of IBD.

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Key Points

- Environmental factors, including diet, may be involved in the pathogenesis of inflammatory bowel disease because of effects on the gut microbiome.
- Recent studies have identified a possible connection between two commonly implicated environmental risk factors for inflammatory bowel disease—dietary pattern and the gut microbiome.
- Bowel rest and exclusive enteral nutrition with defined formulas are commonly utilized therapies for the management of inflammatory bowel disease and the mechanism of action may involve alterations in the intestinal bacterial composition.
- Further studies are required to better characterize the relationship between diet, the gut microbiome, and inflammatory bowel disease and may provide novel information about disease pathogenesis.

Figure 1.

Relationship between diet, the gut microbiota and IBD. Evidence for these relationships is shown adjacent to the solid arrows. Dietary interventions for the treatment of Crohn's Disease are shown adjacent to the dashed arrows - Exclusive Enteral Nutrition (EEN), Restriction Diet (RD), Bowel Rest (NPO) - Further investigation is needed to determine whether or not any observed efficacy from these interventions involves diet-induced alterations in the gut microbiota. GWAS, genome-wide association studies.