Increasing incidence of inflammatory bowel disease in children and adolescents: the significance of the environmental factors

Running title: Environmental and microbial factors affecting inflammatory bowel disease

Sowon Park, MD¹, Yunkoo Kang, MD², Hong Koh, MD, PhD¹, Seung Kim, MD, MS¹
1. Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Severance Pediatric IBD Research Group, Severance Children’s Hospital, Yonsei University College of Medicine, Seoul, Korea
2. Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Wonju Severance Christian Hospital, Wonju College of Medicine, Yonsei University, Wonju, Korea

Correspondence:
Seung Kim, MD, MS
Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Severance Pediatric IBD Research Group, Severance Children’s Hospital, Yonsei University College of Medicine,
50-1 Yonsei-ro, Seodaemun-gu, Seoul, Korea, 03722
Fax: +82-2-393-9118, Tel: +82-2-2228-2050, E-mail: PEDKS@yuhs.ac

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Abstract

Inflammatory bowel disease is a chronic relapsing immune-mediated disease of the intestinal tract. Although its prevalence is investigated to be lower in Asia than in Western countries, the rapid increase in the incidence rate of inflammatory bowel disease has drawn attention to the etiology of inflammatory bowel disease, including genetic susceptibility and environmental factors. Specifically, recent studies concerning dietary treatments and intestinal microbiota suggest that these factors may interact with the immune system, and the imbalance of this relationship may lead to the immune dysregulation in inflammatory bowel disease. The changes in diet or alteration in the composition of intestinal microbiota may be associated with the increasing incidence of inflammatory bowel disease in Asia. Here, we aim to review the recent studies on the role of the diet and intestinal microbiota in inflammatory bowel disease pathogenesis and the results of the investigations performed to modulate these factors.

Keywords: Inflammatory bowel disease, Diet, Microbiota, Fecal microbiota transplantation
Introduction

Inflammatory bowel disease (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC), is an immune-mediated, chronic relapsing, inflammatory condition that mainly affects the gastrointestinal tract.

The incidence and prevalence of IBD is increasing globally. Although reportedly higher in Western countries, a similar trend is now being observed in Asia as well. The prevalence of CD and UC in Canada in 2008 was 255.2 per 100,000 (95% confidence interval (CI), 252.4–258.0) and 259.7 per 100,000 (95% CI, 256.9–262.5), respectively, and the prevalence of CD and UC in the commercially-insured US adult population during 2008-2009 was 241.3 (95% CI, 238.1–244.5) and 263.0 (95% CI, 259.7–266.4) per 100,000, respectively.(1, 2) In European studies, prevalence rates as high as those in North America have been reported.(3) Unlike in Western countries, the epidemiologic data for IBD in Asia is relatively lacking, but the prevalence of IBD in these areas is thought to be lower. In a Japanese study, the prevalence of CD and UC in 2005 was 21.2 (95% CI, 20.8–21.7) and 63.6 (95% CI, 62.8–64.4) per 100,000, respectively.(4) In South Korea, the adjusted prevalence rates of CD and UC per 100,000 in 2005 were 11.24 (95% CI, 9.29–13.18) and 30.87 (95% CI, 27.47–34.27), respectively.(5) However, according to Korean cohort studies, the mean annual incidence rate seems to have increased by more than 100-fold for both CD and UC in the past 20 years.(5)

Increasing occurrences are also being seen in pediatric patients. From 1994 to 2009, the incidence of IBD in children has increased from 9.4 per 100,000 (95% CI, 8.2-10.8) to 13.2 per 100,000 (95% CI, 11.9-14.6) (p < 0.0001).(6)

Various factors seem to contribute to the increase in the global incidence of IBD.(7) These include an increased awareness of the disease, more developed disease surveillance systems, improved accessibility to hospitals and health care providers, and changes of lifestyle towards...
Westernized environment. Although genetic factors appear to play an important role in the pathogenesis of IBD, as shown in Swedish cohort studies on identical twins, environmental changes over the past few decades have been one of the important factors in raising the incidence of IBD in Asia.(3, 8, 9) This is supported by the higher incidence of illness among immigrants who migrate from countries with low incidence to Western countries.(10) The environmental changes and subsequent alterations of intestinal microbiota are regarded to be important in increased prevalence of IBD in Asia. Therapeutic approaches involving these factors show efficacy in recent studies also support this proposition.(11-17) In this review, we will discuss the environmental, nutritional and microbial factors that attribute to the pathogenesis of IBD as well as therapeutic approaches by modulating these factors.

**Diet as an environmental factor**

Dietary patterns and nutritional factors are considered to be important environmental factors in the etiology of IBD, and the compositions of the Western diet have long been suspected of contributing to the development of IBD.(10) This diet is characterized by high levels of fats and refined sugars, and is relatively deficient in fiber and vegetables. Several studies, although many were animal studies, have shown that the Western diet is associated with an increased level of pro-inflammatory cytokines, modulated intestinal permeability, and altered composition of intestinal microbiota that promote chronic inflammation in the gut.(18-21) Sakamoto et al. found a positive association between sweet consumption and CD risk (odds ratio (OR): 2.83, 95% CI: 1.38–5.83) and UC (OR: 2.86, 95% CI: 1.24–6.57).(22) This supports views on the detrimental effects of refined carbohydrates and sweetened beverages in the Western diet on IBD. On the contrary, complex carbohydrates, and fiber-rich vegetables and fruits are thought to be beneficial.(23) Haskey et al. showed that a high
protein intake, especially from animal protein, resulted in a 3.3 times increased risk of IBD, suggesting that a diet high in animal protein was a major risk factor.(23) With respect to the intake of dietary fats, a high n-3 polyunsaturated fatty acid (PUFA) to n-6 PUFA ratio is reportedly inversely associated with the risk of IBD.(23-25) 

There have been several studies showing the influence of certain components contained in food on epithelial cell permeability. For example, Soderholm et al. found that sodium caprate, a medium-chain fatty acid in dairy products, increased intestinal permeability in the ileums of both rats and humans, more noticeably in those with CD.(26, 27) Lammers et al. proved that gliadin, the toxic component of gluten that initiates the inflammatory response in celiac disease, binds to the C-X-C motif chemokine receptor 3 in the small intestinal epithelium to increase zonulin release in a myeloid-differentiation primary-response 88-dependent manner, and subsequently increases intestinal permeability.(28) Increased intestinal permeability is associated with a defective mucosal barrier, and decreased barrier function can allow the exposure of luminal bacteria and their products to the mucosa. An influx of the luminal contents to the intestinal mucosa triggers an immune cell activation and cytokine production or secretion.(29) 

Aside from the nutritional food components, food additives such as detergents and emulsifiers may be associated with defective barrier function.(30) Chassaing et al. documented in an animal study that chronic exposure to carboxymethylcellulose, a widely-used cellulose derivative used as a viscosity modifier in a variety of dairy products, sauces, and sausages, induce increased bacterial adherence to the intestinal epithelium, particularly amore pro-inflammatory microbiota.(31) Another food emulsifier commonly used in processed food, polysorbate-80, increased translocation of Escherichia coli across M cells and Peyer’s patches in patients with CD.(32)
**Intestinal Microbiota and IBD**

The human microbiota consists of about $10^{14}$ diverse microbes, and the colon is the largest reservoir of human microbiota.\(^{(33)}\) The gut microbiota affects human health by performing many roles in metabolite synthesis, barrier function, and immune responses.\(^{(34)}\) There is an interaction between the gut microbiota and the host immune system and, when this balanced relationship is disrupted, gut microbial composition changes occur which consequently aggravate permeability dysfunction.\(^{(35)}\) This, in turn, further aggravates the alteration of microbial composition, i.e. dysbiosis, and a chronic inflammatory response occurs in the host immune system.

The intestinal microbiota is also known to have an important role in the pathogenesis of IBD.\(^{(36)}\) Many studies have shown a lower microbial diversity and a higher microbial dysbiosis index in IBD patients compared to healthy controls. Moreover, a long-term follow-up study of fecal microbiota in patients with IBD showed that the microbial profiles of IBD patients are different to those of healthy controls, and high volatility was observed in IBD patients.\(^{(37)}\)

Some specific changes in the intestinal microbiota of IBD patients have been identified, such as decreases in *Roseburia hominis* and *Faecalibacterium prausnitzii*, the butyrate-producing species.\(^{(38)}\) There are reports of an increased amount of *Enterobacteriaceae* and a reduced number of *Clostridium* clusters IV and XVIa during disease-associated inflammation in newly diagnosed CD patients.\(^{(39)}\) Increases in *Escherichia coli*, *Fusobacterium*, and *Proteus*, as well as reductions in Firmicutes such as *Faecalibacterium prausnitzii* have also been reported.\(^{(3)}\)

In newly diagnosed pediatric IBD patients, an increased amount of Proteobacteria and a decrease in *Faecalibacterium prausnitzii* in the intestinal microbiota seem to be associated
with complicated disease phenotypes, and a subsequent need for biologic therapy or surgery.(40)

**Diet and microbiota**

Colonization of the gut begins at birth, and the gut microbiota become more stable and toward adult-like complexity during the first year of life.(41) Various environmental factors, such as diet, are known to contribute to this phenomenon, which begins very early in life. A higher proportion of *Bifidobacteria* was found in breastfed infants compared to those who are formula-fed.(42) As previously mentioned, dietary patterns are associated with the pathogenesis of IBD, and they are also related to the intestinal microbiota. In a mouse model, mice fed with a high-fat diet demonstrated dysbiosis characterized by an increase in Proteobacteria and a decrease in Firmicutes, which was similar to that observed in CD.(43) A high-fat diet results in the accumulation of secondary bile acids, which in turn can inhibit the growth of the Bacteroidetes and Firmicutes phyla, a common dysbiotic feature found in CD.(44) These varied evidences suggest that the dietary pattern influences the composition of the intestinal microbiota and, through this indirect mechanism, diet can determine subsequent intestinal inflammation (Figure 1).

**Environmental modification as a treatment**

**Dietary modification.**

Exclusive enteral nutrition (EEN) is the only evidence-based dietary treatment of IBD. EEN involves a completely liquid diet without any normal dietary components for a certain period of time. It is used as a therapeutic method to induce remission in pediatric patients with active CD.(45)
According to a meta-analysis, EEN is as effective as corticosteroids in inducing remission in pediatric CD patients. This is true not only for newly diagnosed CD but for relapsed cases as well (OR: 0.76, 95% CI: 0.29-1.98). Furthermore, EEN was found to be more effective than corticosteroids with respect to mucosal healing (OR: 4.5, 95% CI: 1.64-12.32).(46) Based on these results, the European Crohn’s and Colitis Organization and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) consensus guidelines on the medical management of pediatric CD recommended EEN as the first-line therapy to induce remission in children with active luminal CD.(47) Although the mechanisms are not yet fully understood, there is some evidence that EEN reinforces the epithelial barrier and, accordingly, bacterial invasion into the mucosa is prevented. Moreover, strengthening the barrier can restore the intestinal microbial dysbiosis and affect the dysregulated immune system by decreasing pro-inflammatory cytokines, as well as the local action of anti-inflammatory cytokines. By these means, EEN is thought to improve inflammation in CD.(48) Despite the safety and efficacy of EEN in inducing remission in pediatric CD patients, intolerance or poor adherence to EEN is the main hindrance to implement this therapeutic method.(49) Recent randomized clinical trial by Levine et al. showed the combination of Crohn’s disease exclusion diet (CDED) with partial enteral nutrition (PEN) induced sustained remission at week 12 compared to EEN group (75.6% and 45.1% respectively, p value = 0.01). Moreover, significantly higher tolerance was noted in patients who received CDED with PEN compared to the patients with EEN (97.5% and 73.7% respectively, p value = 0.002).(11)

Table 1 shows various attempts to develop a new dietary treatment method in IBD to target the modulation of intestinal microbiota or the immune system itself.(11, 50-60) However, there is still insufficient evidence to propose a recommendation. A recent Position Paper on
Behalf of the Porto Inflammatory Bowel Disease Group of the ESPGHAN also stated that “elimination or restrictive diet in children/adolescents with IBD should not be recommended unless potential benefits outweigh potential risks of the diet.”(61)

Use of probiotics and prebiotics in the treatment of IBD

Ever since intestinal microorganisms were known to attribute to the pathogenesis of IBD, efforts have been made to restore this altered microbial composition. Administration of probiotics and prebiotics as a mean of IBD treatment has been investigated with inconsistent results.(21)

Probiotics are defined as live microorganisms that are, when ingested in adequate amounts, beneficial to the health of host. As derived from commensal microbiota, they mimic the homeostatic effect of intestinal microbiota in healthy condition. They affect the mucosal immune system by balancing pro- and anti-inflammatory components, alter the microbial composition by inhibiting the pathogenic bacteria, and enhance the barrier function.(62-65)

Although many probiotics demonstrated limited efficacy in UC, the probiotic cocktail VSL#3 and Escherichia coli Nissle 1917 showed to reduce active inflammation in many studies.(66-69) They were associated with increased mucosal regulatory T cells, reduced pro-inflammatory cytokines, increased microbial diversity, and restoration of barrier integrity. However, they did not show statistically significant impact in treating CD.(70, 71) In addition, several microbes such as Faecalibacterium prausnitzii and Bacteroidesfragilis have been studied for their therapeutic potential as they seem to be beneficial in reducing the severity of colitis in many mouse models.(72-74)

As shown above, some taxa seem to be associated with the disease course of IBD through the interaction with the immune system.(38-40) However, changes of specific microbiota that
increase risk of IBD are not completely clear. Therefore, it is important not only to manipulate specific microbiota but also to enhance the overall environment of beneficial microorganisms. Moreover, the fact that dietary modification affects the disease course of IBD also suggests the significance of prebiotics as nutrient source of microbiota.

Prebiotics are non-digestible food components fermented by microbiota to elicit advantages to the host. By providing essential food to the microbiota, prebiotics can modify the gut microbial composition and subsequent metabolites. For instance, oligosaccharide and fibers induce proliferation of short chain fatty acid producing bacteria, such as Bacteroides genus, to improve the severity of colitis in IBD.\textsuperscript{(75, 76)} In many in vitro and animal research also confirmed that providing prebiotics help to alleviate the severity of colitis by an alteration of microbial composition, the production of short chain fatty acids such as butyrate, and balances in pro- and anti-inflammatory cytokines.\textsuperscript{(77-80)}

There are several human studies conducted to confirm the efficacy of prebiotics in IBD patients, but the results are controversial. Lindsay et al. showed the reduction of disease activity index and increase of mucosal Bifidobacteria when CD patients were provided with 15 g of fructooligosaccharides (FOS).\textsuperscript{(81)} However, randomized trial conducted by Benjemin et al. showed no significant improvement in disease activity in population who received FOS although there was increase in interleukin (IL)-10 producing desndritic cells (DCs) and reduction in IL-6 producing DCs.\textsuperscript{(82)} Other than FOS, germinated barley foodstuff, Ispaghula husk, and combination of oligofructose with inulin have showed its potential in inducing remission or reduction of inflammation in UC patients, and inulin showed its efficacy in pouchitis patients as well.\textsuperscript{(83-86)}

As describe above, probiotics and prebiotics are thought to play distinct roles in regulation of immune system. Although they are considered feasible armamentaria in modulation of
intestinal microbiota and possible treatment options in IBD, many clinical trials about this subject are tremendously heterogeneous in the study design, mode of administration, and used probiotics or prebiotics to lead to a firm conclusion. Therefore, well-designed further study in larger population is needed in order to find which probiotics or prebiotics are effective in treatment of IBD.

**Intestinal microbiota modification as a treatment; fecal microbiota transplantation**

Another attempt to modulate intestinal microbiota is fecal microbiota transplantation (FMT). FMT is regarded as the most direct method to manipulate the intestinal microbiota profile and there is much on-going research regarding FMT as a potential treatment for IBD.

As the first case of FMT in pseudomembranous colitis was reported several decades ago, FMT has been well studied and proven to be an effective and safe treatment in refractory or recurrent *Clostridium difficile* infection.(87) This has stimulated research in FMT for other diseases related to dysbiosis, including IBD.

Although there are no available randomized controlled trials (RCTs) in CD patients, six uncontrolled cohort studies were reported, with controversial results.(12) Vermeire et al. reported a 0% remission rate in patients with moderate to severe CD, whereas Cui et al. reported a 76.7% clinical remission rate after four weeks of FMT.(13, 14) Although the meta-analysis of the six pooled cohort studies showed a clinical remission rate of 52%, RCTs with a larger number of patients are needed in order to assure the efficacy of FMT in CD patients.(88)

In contrast to CD, larger RCTs have been performed in UC patients. A clinical remission rate of 24-50% has been reported in an FMT group and in three of four studies, remission rates were significantly higher in the FMT group than in the control group.(15-17, 88) Meta-
analysis of four RCTs also showed significant benefit in clinical remission (pooled OR: 2.89, 95% CI: 1.36-6.13, \( p = 0.006 \)).(88) Consequent to these studies, the American Gastroenterological Association has stated the efficacy of FMT in induction of remission in mild-moderate UC.(89)

In pediatric patients, there is no published RCT, but six cohort studies assessing 34 UC patients and two cohort studies assessing 13 CD patients showed a pooled estimated clinical remission rate of 23% (95% CI: 7-51) in UC and 54% (95% CI: 28-78) in CD patients.(88) The clinical trials and their results of FMT in pediatric IBD patients are summarized in Table 2.(90-100)

FMT has been considered a relatively safe treatment modality with a low rate of adverse events, when there was a thorough investigation of donor fecal material. Any reported side effects were mild and self-limiting.(101) Although serious adverse events (SAEs), such as flaring up of the disease, were reported in several studies, recent meta-analysis showed no significant difference between the FMT and the control groups with respect to SAEs. The pooled rate of SAEs was 7.1% in the FMT group versus 5.1% in the control group with no significant difference (risk ratio adverse event: 1.40, 95% CI: 0.55–3.58, \( p = 0.49 \)).(102)

FMT can be considered a relatively safe and effective treatment option in IBD by modulating intestinal microbiota. However, a number of factors affecting the outcome and efficacy of FMT need to be determined, including pretreatment before FMT, dosage and frequency, preparation of donor stools, and routes of administration. Further studies are needed to have a better understanding of FMT and to provide optimal FMT in IBD.(12)

**Conclusion**

Numerous environmental factors can attribute to the increasing incidence of IBD. Of these,
dietary and nutritional factors are considered to be important and to play a role in the pathophysiology directly or through changes of intestinal microbiota. Although this is a “biologic era” in which a variety of new potent medications is being used, modifying causative environmental factors is still expected to have a more fundamental role in treating and preventing IBD. For deeper understanding of IBD, it is necessary not only to focus on the medical management, but also on the understanding and manipulating environmental factors, such as dietary treatment and FMT.

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Figure legends

Figure 1. Relation of diet, intestinal microbiota, and inflammatory bowel disease

Both the genetic susceptibility and diet can account for the incidence of inflammatory bowel disease and microbial composition. Inflammatory bowel disease itself and disease severity are also responsible for the microbial composition, and conversely dysbiosis is also thought to affect inflammatory bowel disease.
Table 1. Summary of the various dietary treatments of IBD other than EEN

<table>
<thead>
<tr>
<th>Diet</th>
<th>Composition and rationales of the diet</th>
<th>Literatures</th>
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<tbody>
<tr>
<td>Specific carbohydrate diet</td>
<td>Diet originally developed for Celiac disease which excludes complex carbohydrates and processed foods to improve intestinal inflammation by restoring microbial diversity</td>
<td>Case series, Prospective studies, Retrospective studies</td>
</tr>
<tr>
<td>CD-TREAT diet</td>
<td>Individualized and revised version of EEN that mimics the composition of EEN using ordinary food</td>
<td>Prospective study</td>
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<td>Crohn's disease</td>
<td>Avoidance of sauces except some specific spices and herbs, gluten, dairy products, gluten free baked goods and breads, animal fat, processed meats, food products containing emulsifiers, canned goods, and all packaged products which hypothetically affect the microbiome or intestinal permeability.</td>
<td>Observational studies, Prospective studies</td>
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<td>Exclusion Diet (CDED)</td>
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<tr>
<td>IBD-AID (Anti-inflammatory diet)</td>
<td>A nutritional regimen as an adjunctive dietary therapy for IBD that restricts the intake of certain carbohydrates, but includes pre- and probiotic food, modified dietary fatty acids and food texture</td>
<td>Retrospective case series</td>
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<td>IgG4 exclusion diet</td>
<td>Diet excluding food with high IgG4 titer</td>
<td>RCTs</td>
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<tr>
<td>Low FODMAP diet</td>
<td>Avoidance of poorly absorbed short-chain carbohydrates in order to elude bacterial fermentation or water shedding into the lumen</td>
<td>Pilot study, RCTs</td>
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<tr>
<td>Author</td>
<td>No. of patients</td>
<td>Severity</td>
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<tr>
<td>Kunde et al., 2013(92)</td>
<td>10</td>
<td>Mild-Moderate (PUCAI 15-65)</td>
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<tr>
<td>Kellermayer et al., 2015(93)</td>
<td>3</td>
<td>Immunotherapy dependent but controlled (Mayo 0-1)</td>
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<tr>
<td>Vandenberg et al., 2015(94)</td>
<td>1</td>
<td>Severe (PUCAI 60-75)</td>
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<td>4</td>
<td>Mild-moderate (PUCAI 20-55)</td>
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<tr>
<td>Shimizu et al., 2016(96)</td>
<td>1</td>
<td>Severe, steroid dependent UC</td>
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<td>Severe (PUCAI 85)</td>
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<td>8</td>
<td>Moderate-Severe (PUCAI 15-70)</td>
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<td>Goyal et al., 2018(100)</td>
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<td>Mild-moderate (PCDAI &lt;40)</td>
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<td>Mild-moderate (PCDAI 10-29)</td>
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