Role of Diet in Inflammatory Bowel Disease

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Abstract

The incidence of inflammatory bowel disease (IBD) is steadily on the rise in Western as well as in developing countries paralleling the increase of westernized diets, characterized by high protein and fat as well as excessive sugar intake, with less vegetables and fiber. An interesting hypothesis is that environmental (food-) triggered changes of the intestinal microbiome might cause a proinflammatory state preceding the development of IBD. Indeed, an intact intestinal epithelial barrier assuring a normal bacterial clearance of the intestinal surface is crucial to guarantee intestinal homeostasis. Any factors affecting the epithelial barrier function directly or indirectly may impact on this homeostasis, as well as any changes of the intestinal microbial composition. It is intriguing to learn that some frequently used food components impact on the quality of the intestinal barrier, as well as the composition of the intestinal microbiome. This highlights the close interaction between living conditions, hygiene, food habits and food quality with the bacterial composition of the intestinal microbiome and the activation status of the intestinal immune system. There is clear evidence that nutritional therapy is highly successful in the treatment of Crohn’s disease (CD). Exclusive enteral nutrition is well established as induction therapy of CD. New diets, such as a CD exclusion diet or defined diets (specific carbohydrate diets, FODMAP diet, Paleolithic diet) are being discussed as treatment options for IBD. Well-designed clinical trials in IBD are urgently required to define the precise role of each of these diets in

Key Messages

- The number of new inflammatory bowel disease (IBD) patients is steadily increasing, especially in countries with a Western lifestyle.
- There is an evident link between the change of food habits/food production and the incidence of IBD.
- Experimental studies indicate that commonly used food ingredients can alter the intestinal barrier, thereby causing intestinal inflammation.
- Complex carbohydrates, such as maltodextrin, emulsifying agents or thickeners, such as carboxymethyl cellulose, carrageenan and xanthan gum were shown to have detrimental effects on intestinal homeostasis.
- Based on epidemiological and experimental studies, exclusion or defined diets were proposed.
- There is good evidence that exclusive enteral nutrition is a potent therapy to induce remission in patients with Crohn’s disease.
- For exclusion and defined diets to treat IBD, scientific proof is still lacking, but interesting studies are underway.

Key Words

Pediatric inflammatory bowel disease · Crohn’s disease · Ulcerative colitis · Enteral nutrition · Diet · Specific carbohydrate diet · FODMAP diet

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the prevention or management of IBD. Up to now, the role of diet in IBD is highly undermined by lay and anecdotal reports without sufficient scientific proof.

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Introduction

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases involving potentially the entire gastrointestinal tract. Most often, the onset of IBD is during young adulthood, but in 15–20% of patients the disease starts before their 18th anniversary [1, 2]. Based on clinical, endoscopic, but also immunological and biological parameters, different phenotypes of IBD can be identified [3]. Usually, the presence of granulomatous lesions and/or the involvement of the small bowel with typical ulcerations orientate towards the diagnosis of Crohn’s disease (CD), while isolated continuous colonic involvement is in favor of ulcerative colitis (UC). The recent modification of the Porto criteria for the diagnosis of pediatric IBD provides a helpful tool in the diagnostic workup and classification of children/adolescents with IBD [4]. When discussing different treatment options for IBD, it is important to consider pathophysiological aspects and differences and to base therapy whenever possible on pathophysiological mechanisms. This approach will allow going beyond symptomatic therapy, yet is still important to relief symptoms, but most often not appropriate to change the course of a chronic disease. Indeed, IBD are chronic inflammatory diseases with a tendency to cause intestinal damage, especially when the disorder starts early in life, i.e. childhood or adolescence. Thus, treatment strategies aim to control this chronic inflammatory process and are mainly based on immunosuppressive agents; however, there are clear indicators that nutritional interventions might also play an important role in controlling IBD.

Major advances have been achieved over the last 15 years in the understanding of the pathophysiology of IBD. There is clear evidence that in genetically determined individuals (over 160 IBD susceptibility genes identified so far [5]), a disruption of the intestinal tolerance occurs towards commensal bacteria. While the carriage of IBD risk alleles alone does not determine disease onset, one or several additional, probably exogenous factors must be present. One key question is if this inappropriate and uncontrolled inflammatory response towards the intestinal microbiome is secondary to an acquired change of the microbial composition. Indeed, in patients with IBD, a marked dysregulation of the colon-ic and intestinal microbiome, called ‘dysbiosis’, is observed, commonly characterized by a decrease in Firmicutes, an expansion of Proteobacteria, along with a decrease in community richness [6]. Alternatively, could a subtle immune defect occur in one or several control steps, crucial for the maintenance of normal intestinal homeostasis, which subsequently might cause a change of the intestinal bacterial composition? It is possible that both factors could contribute to the onset and maintenance of inflammation: the type of immune responses of the host as well as the composition of the intestinal microbiome, which is the preferred hypothesis of the author.

The type of immune responses of the host as well as the composition of the intestinal microbiome could both contribute to the onset and maintenance of inflammation

The observation of a marked increase of the incidence of IBD in general and pediatric forms, in particular over the past 50 years (fig. 1), is a major argument favoring environmental changes as crucial trigger factor for the development of IBD. Genetic factors cannot change within such a short time frame, the disease susceptibility remains almost identical over few generations, but the raised IBD incidence in countries with a Western lifestyle clearly points out to a modification of the lifestyle as main driver of the development of IBD [3]. What are the changes that may disrupt the intestinal homeostasis and thus lead to the increase of IBD? Top research addressing this question is currently underway and some aspects will be reviewed in this article.

Over the last years, it has become clear that intestinal homeostasis (fig. 2) requires a balanced interaction between the intestinal immune system (with innate and adaptive immune responses) and the microbiome. An intact intestinal epithelial barrier assuring a normal bacterial clearance of the intestinal surface is crucial to guarantee this homeostasis. Any factors affecting the epithelial barrier function directly or indirectly may impact on this homeostasis, as well as any changes of the intestinal microbial composition. It is intriguing to learn that some frequently used food components impact on the quality of the intestinal barrier, as well as on the composition of the intestinal microbiome. This highlights the close interactions between living conditions, hygiene, food habits
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**Fig. 1.** Worldwide increase of the incidence/prevalence of CD over the last 50 years. Modified from Molodecky et al. [63].
and food quality with the bacterial composition of the intestinal microbiome and the activation status of the intestinal immune system.

Based on these pathophysiological aspects, it is easily understandable that research recently started to focus on the impact of food on the pathophysiology of IBD, and, perhaps even more important, the role of food or diets in treating IBD [7, 8].

**Food Components, Intestinal Barrier Functions and Inflammation**

**Epidemiological Studies**

A recent Canadian study in children with IBD revealed indeed an imbalance in consumption of fatty acids, vegetables and fruits and the development of CD [9]. Several ecologic prospective cohort studies confirmed the association between both high fatty acid and protein intake with the risk of developing IBD [10–14]. Increased dietary fibers intake has been associated with a lower risk of developing CD, but not UC [15]. There are interesting studies indicating that a specific bacterial pattern (enterotype), characterized by *Prevotella* and *Xylanibacter*, is highly efficient at fermenting dietary fibers, thereby leading to higher concentrations of short-chain fatty acids [16], potentially protective against bowel inflammation. It is intriguing to see that *Prevotella* and related bacteria are more frequently present in children from rural Africa where IBD and particularly CD are uncommon [17]. Data on increased sugar and refined carbohydrate intake and the development of IBD are intriguing but currently less clear and there is a striking difference between epidemiological data (with some contradictory findings) and experimental data.

**Experimental Studies**

Recent research indicates that several food additives, such as maltodextrin (MDX), emulsifying agents or thickeners, such as carboxymethyl cellulose (CMC), carrageenan, and xanthan gum, can have detrimental effects on intestinal homeostasis. In vitro experiments with MDX revealed an impaired anti-bacterial response of macrophages and epithelial cells when MDX was in the culture medium, as was demonstrated by the increased viability of intracellular *Salmonella* [18]. Any MDX dose was able to produce this effect, with higher doses having a greater effect on bacterial viability. In vivo studies in preterm piglets indicate that MDX consumption leads to the expansion of ileal *Escherichia coli* and induced necrotizing enterocolitis in these animals [19]. This observation is particularly interesting in the light of the fact that in CD patients, a dense ileal mucosal population with an adherent invasive form of *E. coli* (AIEC) is documented [20]. This AIEC colonization is considered as one key
trigger of ileal inflammation in CD patients. Experimental data revealed a direct positive effect of MDX on *E. coli* (including the AIEC strain) cellular adhesion and biofilm formation. Thus, it is very tempting to speculate about MDX-promoted colonisation and MDX-increased survival of mucosal *E. coli* in patients susceptible to develop CD. In addition, a recent study documented an enriched MDX microbial metabolism in patients with ileal CD, in contrast to colonic CD patients and non-IBD controls [21]. This is even more intriguing when we consider that since the mid-50s, MDX has increasingly been used as thickener, texturizer, or coating agent, and today more than two thirds of packaged food products contain MDX or 'modified starch' (corn, wheat, etc.), paralleling the increased incidence of IBD since World War II.

Not only MDX or modified starches impact on the intestinal homeostasis; other dietary additives, such as emulsifiers or thickeners (used to stabilize prepared foods or to modify/ameliorate product texture and viscosity) were also shown to contribute to intestinal barrier dysfunction. Examples are carrageenan, CMC or xanthan gum, which are derived from natural products and are so far classified as safe (currently under reconsideration). Already in 1990, experiments in rodents indicated that carrageenan can induce intestinal inflammation [22]. In the same line, CMC consumption results in bacterial overgrowth and more aggressive inflammation in interleukin-10-KO (deficient) mice [23]. These emulsifiers act directly on the mucosal barrier by decreasing the viscosity of the mucus, thereby facilitating bacterial translocation and potentially driving inflammation [24]. This mechanism on the barrier function is well-known and frequently used as mechanism for experimental colitis [25]. Based on these considerations, it is not surprising that restriction diets or nutritional interventions have become very attractive for the treatment of IBD.

**Role of Food/Diet in the Treatment of IBD**

The best and strongest evidence for the potential to treat IBD with a specific nutritional intervention comes from the use of enteral nutrition (EN) as induction therapy for CD. Initially, EN was used as supplemental nutritional therapy in undernourished adult patients prior to resection surgery for CD. This nutritional intervention revealed to be very efficacious and to have anti-inflammatory effects finally making surgery unnecessary in some patients. It rapidly became clear that EN, used on an exclusive basis, is a potent anti-inflammatory treatment, highly efficacious to induce remission in patients with CD [26]. However, patients with UC seem not to respond to exclusive enteral nutrition (EEN) [27]. Other nutritional interventions are currently discussed and tested, since more and more patients are interested in controlling their IBD with nutritional interventions instead of using immunosuppressive agents.

**Efficacy of EEN as Treatment Option for CD**

**Induction of Remission of CD**

EEN has a strong and rapid anti-inflammatory effect in patients with CD, with reduction of systemic and mucosal inflammatory parameters within a few days of initiation [28]. No randomized controlled trial (RCT) compared EEN to placebo in children with CD. However, two pediatric meta-analyses as well as a Cochrane review (combining pediatric and adult data) analyzed the efficacy of EEN as induction therapy for CD compared to steroids [29–31]. Clinical trials comparing EEN to steroids based on remission rates as outcome parameter showed an overall remission rate of approximately 75% for EEN at the end of exclusive treatment. Remission rates with steroids were not different from EEN-induced remission in these two meta-analyses based on a total of 11 pediatric clinical trials [32–41]. A further pediatric study has recently been published [41], showing data in line with the previous studies. It is somewhat challenging to summarize the efficacy of EEN based on these open-label studies, since there are major differences in how EEN is performed (duration, feed types, as well as outcome measures) [42, 43]. Two recent large single-center studies, each based on more than 100 pediatric CD patients, further support the results of the clinical trials, each one showing a remission rate of approximately 80% [44, 45]. Six different studies analysed the potential of EEN to induce mucosal healing, with healing rates from 19 to 75% [28, 38, 45–48]. The definition of mucosal healing differs between the studies, making them difficult to compare. The rate of mucosal healing was clearly higher in patients on EEN compared to those with steroid-induced remission [38, 46]. One RCT included mucosal healing as outcome parameter, indicating a clear superiority of 10 weeks of EEN compared to steroids, with mucosal healing rates of 74 and 33% for EEN and steroids, respectively [49].

Data from adult patients are not in keeping with the pediatric studies and rates to induce remission with EEN are lower, probably due to lower adherence to the exclusivity principle and also less experience among adult-IBD experts with the use of this nutritional intervention. The best results for EEN occur in IBD centers that regularly
use EEN as treatment option, while remission rates differ significantly in centers that rarely or almost never use EEN.

Different liquid nutritional products are available and were tested in the treatment of CD showing its efficacy in children and adult patients [39–41], as demonstrated by RCTs [27–29, 34]. Efficacy does not depend on the protein source; polymeric or elemental feeds equally induce remission in CD patients, while acceptability as well as costs of EN differ markedly between elemental diets or polymeric feeds: elemental feeds are less often tolerated by mouth and patients often choose nasogastric tube administration. In contrast, for patients receiving polymeric feeds, the oral route is most often the first choice [44].

We have recently demonstrated that there is no significant difference in remission between oral- and continuous nasogastric tube-induced feeds [44]. Therefore, in our center, according to the recent pediatric guidelines, we always offer oral feeds with a polymeric formula, while EEN via a nasogastric tube remains reserved for patients unable to achieve the desired caloric intake or who refuse oral feeding due to taste or texture [50]. Elemental feeds should only be reserved for patients allergic to cow’s milk proteins. As many patients have weight loss and/or growth retardation, the estimated energy requirements are above the recommended intake. Therefore, we most often use 120% or more of the normal caloric requirements adjusted to age and estimated needed catchup growth.

The most important point when using EN as induction therapy is to use it on an exclusive basis, without any additional foods. Johnson et al. [51] showed in a RCT (exclusive EN vs. partial EN with normal diet over 6 weeks using an elemental formula) clear superiority for full EEN over partial EN in remission rates at 6 weeks [10/24 (42%) vs. 4/26 (15%), respectively]. In that study, efficacy of EEN was markedly lower than in most other published studies, and there was a high dropout rate in both arms, highlighting the relevance of compliance. Compliance a priori is not any better in children than in adult patients, but marked growth retardation and the potential of EEN to allow efficient catchup growth is a major motivation for children and adolescents with CD. Close monitoring and regular home visits by a dietician or nurse further improve the successful use of EEN.

Maintenance of Remission in CD

The role of maintenance therapy based on EN is less clear. Several studies analyzed the potential of nutritional supplementation as long-term therapy (alone or in addition to standard therapy). A recent meta-analysis [52] highlighted that overall clinical remission rates were higher in patients with EN than in those without. The quantity of enteral formula used was shown to be important: higher amounts of enteral formula were associated with higher remission rates. However, large RCTs are necessary to assess a definite role of EN for the maintenance of remission.

The mode of action of EN to treat CD is still not completely understood despite many ongoing studies. Several mechanisms have been proposed: reduced allergenic load, being nucleotide free, no addition of food additives, and an anti-inflammatory lipid composition. In line with the mechanisms discussed above, a new hypothesis has recently been developed in that EEN has a specific effect on the intestinal microbiome, positively interfering with the dysbiosis in CD patients. Some studies analyzed changes in the microbiome during and after EEN [53, 54].

Defined Diets for IBD

Defined diets are dietary interventions or regimens based on an underling theory or ideology on how food interacts with specific body functions. There are some anecdotal reports on how diets can positively interfere with the course of IBD, such as specific carbohydrate diets, FODMAP diet, CD exclusion diet or the Paleolithic diet.

The specific carbohydrate diet (SCD) was introduced and initially described in the early 1920s to treat celiac disease. In the years that followed, it became very popular due to several impressive lay reports indicating the potential of SCD to cure various diseases, including UC. The underlying theory of the SCD is that disaccharide and polysaccharide carbohydrates are poorly absorbed in the human intestinal tract, resulting in bacterial and yeast overgrowth. This might lead to an inflammatory stimulation with mucosal damage, subsequently causing an aggravation of carbohydrate malabsorption and a vicious auto-amplifying cycle. Thus, the recommendation is to restrict carbohydrate exposure to the monosaccharides glucose, fructose, and galactose. However, today significant variations of a carbohydrate-free (reduced) diet exist. For example, a less strict version is a gluten-free diet. These effects are hypothesized to result in small bowel injury, thus perpetuating the cycle of carbohydrate malabsorption and intestinal injury. A very recent retrospective study [55] in 26 children with IBD indicated that the use of a specific carbohydrate-free diet is potentially helpful in maintaining remission, as highlighted by a marked drop in disease activity scores. It is important to mention...
that most patients remained on maintenance drug therapy and only one half of the patients had a strict SCD.

The FODMAP diet’s rationale is close to that of the SCD in that poorly absorbed carbohydrates (fermentable oligo-, di- and mono-saccharides and polyols, FODMAPs) result in intestinal bacterial overgrowth, a reduced intestinal barrier and secondary mucosal inflammation [56]. However, despite this overlap, there are significant practical differences: the FODMAP diet is highly restrictive of certain fruits and vegetables, while the SCD has unrestricted fruit and vegetable intake except for potatoes and yams. So far, only two studies evaluated the role of FODMAP diet in IBD, 1 in 8 UC patients after colectomy [57], the second was a retrospective study in 72 adult IBD patients [58], indicating a significant effect of reducing abdominal pain, bloating and stool frequency, as long as patients were adherent to the diet. A prospective evaluation of 5 patients after colectomy for UC failed to show any benefit from a reduction of FODMAPs in the diet [57].

An innovative nutritional approach is based on partial EN plus a very strict exclusion diet avoiding animal fat, high sugar intake, gliadin, and consumption of emulsifiers and maltodextrin [7]. In a pilot study of 47 CD patients [59] (34 children and 13 adult patients), excellent response and remission rates were obtained (79 and 70%, respectively). Normalization of previously elevated C-reactive protein occurred in 70% of the patients who achieved remission. A RCT that further elaborates on the role of this CD exclusion diet as a new treatment option is underway.

Another approach is the so-called Paleo diet, which was rediscovered from a publication in the New England Journal of Medicine in 1985 [60]. This diet is based on an evolutionary hypothesis that the human digestive tract is insufficiently evolved to handle foods resulting from modern agricultural techniques. The exposure of the human digestive tract to foods that were not present at the time of human evolution may result in modern diseases. The Paleo diet privileges the intake of lean, non-domesticated meats and non-cereal plant-based foods (i.e. fruits, roots, legumes, and nuts). So far, no data on the role of the Paleo diet in the treatment of IBD exist.

One important flipside of these diets, besides their very restrictive character, is the potential of creating deficiency of particular nutrients, especially vitamins. Both the SCD and the Paleo diet have the potential to cause vitamin D deficiency. This is a particular concern, given the importance of sufficient vitamin D levels for normal immune function, particularly in the gastrointestinal tract. Vitamin D deficiency was recently associated with an increased risk of surgery and hospitalization in IBD patients [61].

An internet search of dietary recommendations for patients with CD indicated that references to vegetables, fruits, and fibers were particularly common. For instance, avoidance of fatty and fried foods was unanimously indicated for CD and in over 70% of sites specifically for UC [62]. Avoidance of raw vegetables, cruciferous vegetables, citrus fruit, red meat, carbonated beverages, coffee and tea, alcohol, fatty and fried foods, spicy foods, sugars, seeds, and popcorn were also often mentioned, while an increased intake of cooked vegetables, fish, poultry, lean protein, and a high-protein diet were also frequently recommended. The authors concluded that ‘our web search analysis demonstrated that patient-targeted dietary recommendations are highly restrictive and frequently conflicting. These recommendations may result in patient confusion and unnecessarily restrictive diets’. This analysis nicely summarized the desperate search of many patients for dietary/nutritional interventions for CD and UC. This is a promising concept, but it has to be based on the pathophysiological aspects of the disease, rather than ideological believing and nutritional recommendations. It has to be based on well-designed and performed clinical trials. It is encouraging that several trials are planned or already underway telling us in the near future what might be the most efficient way to treat our patients with IBD, presumably in a personalized way combining nutritional and medical strategies.

**Disclosure Statement**

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