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Nutritional interventions for the treatment of IBD: current evidence and controversies

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***Abstract*:** Environmental factors, particularly diet, are the focus of current research as potential triggers of inflammatory bowel disease (IBD). Epidemiological cohort data showing a rapid increase of IBD in western countries and the emergence of IBD in developing countries paralleling the introduction of a western diet are indirect arguments linking food and food behaviour to intestinal inflammation. The successful use of exclusive enteral nutrition (EEN), now considered as first-line induction therapy for paediatric Crohn's disease (CD), is the strongest argument for a link between diet and IBD. Mechanistic studies revealed that EEN impacts intestinal microbiota composition and together with the exclusion of potentially harmful food ingredients this allows the control of intestinal inflammation and induces mucosal healing. However, the exclusivity character of EEN is a major drawback. Based on the data of EEN, the search for more tolerable and still effective diets has begun. Recent reports on the new CD exclusion diet (CDED), CD-TREAT, as well as the specific carbohydrate diet (SCD) provide the first promising results, further underlining the potential of diet to control inflammation in patients with CD by excluding certain food components. Ongoing research is trying to combine nutritional interventions with analyses of intestinal microbiota and their metabolic functions with the aim of correcting the intestinal dysbiosis that characterizes IBD. This research is promising and gives new hope to patients that have been looking for decades for nutritional interventions with the aim of stabilizing their disease course. There might even be potential for disease prevention in high-risk patients by excluding potentially harmful food components.

Keywords: Crohn's disease, inflammatory bowel disease, pediatric, exclusive enteral nutrition, Crohn's disease exclusion diet, specific carbohydrate diet

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The role of diet in the pathogenesis of IBD

Crohn's disease (CD) and ulcerative colitis (UC) are chronic intestinal inflammatory diseases of unknown aetiology, characterized by a recurrent inflammatory condition. The pathophysiology is multifactorial and complex, involving an inappropriate immune activation of the gut mucosa in genetically susceptible individuals, triggered by an altered composition of the gut microbiota. The incidence of inflammatory bowel disease (IBD) has increased worldwide in developed nations and more recently in developing countries.[1,2] This rapid increase in the incidence of IBD over the last half-century, particularly in developing countries, clearly points to the role of changing environmental factors intrinsically implicated in disease development.[1] Genes cannot change within such a short time frame, thus disease susceptibility remains almost identical over several generations. The differing role of genetics and the environment in disease development is clearly reflected by epidemiological data on immigrants from low- to high-IBD-incidence regions: where, the second generation of immigrants has the same risk of developing IBD as the local population living for generations in the same area.[3] A western lifestyle, including changes in dietary habits, urbanization and industrialization, has been proposed as one explanation for this worldwide increase in IBD.[4]

Among environmental factors, diet is widely thought to play a pivotal role in the development of IBD. Epidemiological studies suggest a western diet, high in fat and protein content and low in fruits and vegetables, as a possible explanation for the recent increase in IBD.[5] It is important to address the question of whether there is a particular window of vulnerability/susceptibility to developing IBD with regard to a particular dietary exposure during infancy, childhood or adulthood or whether the simple and prolonged exposure to certain food components is a risk factor *per se*. Several large longitudinal studies have demonstrated an association between a reduced risk of developing IBD and a diet rich in fruits and vegetables, whereas consuming high amounts of animal fats and refined sugar is associated with an increased IBD risk.[6–8] Epidemiological studies indicate a higher consumption of red and processed meat, dietary fat and low levels of vitamin D are associated with an increased risk of developing IBD.[7,9,10] During recent decades, a shift in the composition of the daily diet occurred with a greater proportion of processed, prepackaged foods high in fat and carbohydrates, and low in dietary fibre. The evolutionary hypothesis has recently emerged developing the idea 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. One example largely supporting this hypothesis is the use of emulsifiers in current foods. Emulsifiers are added to most processed foods to enhance taste, aid texture and extend shelf life. Chassaing and colleagues[10] demonstrated that emulsifiers induce a chronic intestinal inflammatory state promoting the development of chronic colitis in susceptible mice. In this experimental work, the intestinal microbiota were critical in triggering inflammation, since germ-free mice did not develop colitis upon exposure to emulsifiers. Another example is the food additive carrageenan, largely used in western foods to improve the texture. The proinflammatory character of carrageenan is well known and a recent small randomized trial in adult patients with UC[11] showed a relapse in three out of five patients exposed to carrageenan compared with none out of seven patients on a carrageenan-free diet.

The triple interaction between diet, intestinal microbiota and the host

The effects of nutrition and diet on the host are multiple: food ingredients can directly interact with epithelial cells or under certain conditions with the immune system, as well as indirectly *via* gut microbiota. Gut microbiota form a complex and dynamic system with a steady state, which can be perturbed by many environmental factors, including diet. A homeostatic balance of the host–bacteria relationship is important and vital for a normal health process. An imbalanced intestinal microbiota termed 'dysbiosis' has been repeatedly seen in IBD and is now recognized as a key factor in gut inflammation.[12] Sokol and colleagues[13] showed a significant decrease in the proportion of the *Clostridium leptum* phylogenetic group in patients with colonic CD. These results were confirmed by a metagenomic approach, revealing a restriction in biodiversity depending on bacteria belonging to the Firmicutes phylum (*C. leptum* and *Clostridium coccoides*) with a decrease in the proportion of bacteria belonging to the *C. leptum* phylogenetic group.[14,15] This dysbiosis is characterized by a high instability of the microbiota over time, the presence of approximately 30% of unusual bacteria, a marked increase in mucosal bacterial concentration, and a restriction in biodiversity regarding the Firmicutes phylum. Within this group, a decrease in *C. leptum* has been shown and particularly its major representative, *Faecalibacterium prausnitzii*.[12]

Dietary habits are one of the main factors contributing to the diversity of human gut microbiota. Diet may directly affect the microbiome, thereby modifying the interaction with the host.[16] A study from De Filippo showed that gut microbiota from children with high fibre intake living in a rural African village in Burkina Faso, an environment resembling that of Neolithic subsistence farmers, is significantly different from the microbiota of children living in the urban western world with an enrichment in Bacteroidetes and particularly *Prevotella* spp. and *Xylanibacter* spp., but fewer Firmicutes in African compared with European children.[17] A fibre and plant-derived polysaccharide-rich diet in children and adults is associated with human gut microbiota enriched in Bacteroidetes compared with Firmicutes.[16,17] High-fat diets were shown to increase bowel permeability through dietary-induced changes in the

gut microbiota.[18] High-fat diets also worsen dextran sodium-sulphate-induced (DSS) colitis in mice, possibly by increasing colonic epithelial nonclassical natural killer T cells and reducing regulatory T cells.[19] Llewellyn and colleagues,[20] using a mouse model of colitis to control the host genotype and the gut microbiota, tested the effect of more than 40 dietary combinations on the severity of colitis induced by DSS. They found that faecal microbiota varied with diet and that the concentration of protein and fibre had the strongest effect on the development of colitis.

The gut microbiota continually produces a diverse repertoire of metabolites from fermentation of both exogenous and endogenous sources.[21] These metabolites serve as important signals that contribute to the regulation of the host physiology and maintenance of health. A role for dietary fibre in the predisposition to IBD appears to have particularly compelling biological plausibility. For example, the fermentation of nondigestible carbohydrates stimulates the growth of bacterial short-chain fatty acid (SCFA) producers. SCFAs mediate a number of important functions for the host, including use as an energy source by intestinal epithelial cells, and a variety of anti-inflammatory properties in T cells, regulatory T cells, neutrophils, and macrophages, where they affect migration, cytolytic activity, cytokine production, and epigenetic regulation of gene expression.[22] In addition, fibre plays a vital role in the maintenance of normal intestinal barrier function.

Diet may also have an impact on the mucosal layer of the digestive tract. Recent studies have demonstrated that microbiota can influence the properties of the colonic mucus layer.[23] Some bacteria possess various enzymes allowing them to degrade and metabolize specific glycans of the intestinal mucosal layer. Desai and colleagues[24] demonstrated that low-fibre diet promotes expansion and activity of colonic mucus-degrading bacteria and that fibre-deprived gut microbiota promote aggressive colitis by an enteric pathogen.

Another mechanism of dietary interaction with the host is *via* a direct effect on the immune system, where dietary antigens by themselves may trigger an immune response. The typical western-style diet, high in sugar and saturated fats and low in fibre, can lead to systemic low-grade inflammation, as described in obesity.[25] In animal models, the consumption of milk-derived saturated fats alters bile acid composition, allowing for a bloom of sulphate-reducing bacteria, which in turn can produce greater amounts of the potentially mucosal toxic hydrogen sulphide and production of helper T cell (Th1) proinflammatory cytokines.[26]

Because dietary antigens, along with bacterial antigens, are the most common types of luminal antigen, it is reasonable to suppose that dietary factors may play an important role in the pathogenesis of IBD, possibly by interacting with both gut microbiota and the mucosal immune system. Current IBD therapies predominantly target the pathological immune responses rather than any potential causal factors on top of the inflammatory cascade. Given that diet is a modifiable environmental risk factor, it has become an attractive target both for the prevention and treatment of IBD.

Nutritional interventions: what is known?

Nutrition for induction of remission. Nutrition plays a significant and well-established role in the treatment of CD, particularly in paediatrics. The most studied dietary intervention in IBD is the use of exclusive enteral nutrition (EEN). EEN was the first clinically validated nutritional intervention to treat IBD, specifically CD, and EEN is the recommended first-line therapy for active paediatric CD in Europe and North America.[27,28] Two paediatric meta-analyses as well as a Cochrane review (combining paediatric and adult data) analysed the efficacy of EEN as induction therapy for CD compared with steroids[29–31] and concluded that EEN is effective in inducing clinical remission in the majority of patients, at a rate comparable with oral steroids. A more recent paediatric meta-analysis published by Swaminath and colleagues,[32] analysing eight studies ($n = 226$ patients with CD treated with EEN and $n = 225$ patients with CD treated with steroids) confirmed that there is no statistically significant difference between both treatment options to induce remission in CD.

The majority of studies are of a retrospective nature or are cohort studies. Yet, three randomized controlled trials were conducted comparing enteral nutrition with oral steroids: the first randomized trial by Sanderson and colleagues[33] showed in 15 children that an elemental diet was as equally effective in inducing remission as steroids. Borelli and colleagues[34] confirmed this finding, comparing patients on a 10-week course of

either an oral polymeric diet with MODULEN IBD® ($n=19$) or oral methylprednisolone ($n=18$), similarly to the recent report of Pigneur and colleagues[35] using an 8-week course of MODULEN IBD® ($n=13$) *versus* oral prednisolone ($n=6$). Despite a comparable clinical efficacy, EEN has a markedly higher potential to induce mucosal healing than steroids. This is of the utmost importance, since mucosal healing is recognized as the main target in patients with IBD, predicting an improved long-term outcome compared with patients not achieving mucosal healing while being in clinical remission. Borelli and colleagues[34] combined a histological and endoscopic score (CDEIS) to evaluate the potential of inducing mucosal healing on corticosteroids *versus* enteral nutrition therapy; they observed a mucosal healing rate of 74 *versus* 33% in enteral nutrition *versus* patients treated with corticosteroids. In keeping, our recent study[35] revealed a significantly higher rate of mucosal healing in patients treated with EEN compared with patients treated with steroids: 89 *versus* 17% ($p<0.005$). These findings clearly favour nutritional induction therapy over steroid medication. Enteral nutrition is less used in adult patients with IBD, although several studies have highlighted its efficacy; however, the Cochrane analysis suggests that corticosteroid therapy may be more effective than enteral nutrition for the induction of clinical remission in adults with active CD.[30] The lack of palatability of enteral formula leads to difficulties in acceptance and compliance especially in adult patients. EEN is usually used when steroids are contraindicated or in a perioperative setting.

It is interesting to note that different types of enteral formula, elemental, semi-elemental and polymeric diet, all share the same efficacy in inducing remission when used on an exclusive basis. The Cochrane meta-analysis of 10 trials did not show any statistically significant difference between patients treated with an elemental diet ($n=188$) and a semi-elemental or polymeric diet ($n=146$).[30] However, the mechanism of EEN action remains unclear; many hypotheses have emerged and several mechanisms have been proposed such as, reduced allergenic load, being nucleotide free, no addition of food additives, and an anti-inflammatory lipid composition. In addition, in line with the mechanisms discussed above, a new hypothesis has recently been developed in that EEN has a specific effect on the intestinal microbiota, positively interfering with the dysbiosis in patients with CD.[35,36] We observed that in children treated with MODULEN IBD® on an exclusive basis, the intestinal microbiota shifted towards a profile with a predominance of *Ruminococcus* and *Clostridium* after successful EEN, extending previous reports.[37,38]

Nutrition for maintenance of remission. In contrast with the well-established data on the potential of nutritional therapy to induce remission in active CD, limited data exist on the potential of dietary interventions to maintain remission. Cyclic administration of enteral nutrition tested in an open trial on eight children with CD markedly reduced the requirement of corticosteroids suggesting a role of dietary interventions as maintenance therapy.[39] Tagaki and colleagues[40] analysed the potential of daily partial enteral nutrition (50% of caloric support) in addition to a continued immunosuppressor (azathioprine) or anti-inflammatory therapy in adult patients with CD in remission. Supplementation with an elemental diet resulted in a reduced relapse rate from 64% to 34% in this trial. In the same line, the open pilot trial of Verma and colleagues[41] showed, in a heterogeneous cohort of adult patients with CD, that nutritional supplementation in addition to anti-inflammatory or immunosuppressive therapy had a beneficial effect allowing an increase in the rather low remission rate from 26% to 48%. Yamamoto and colleagues[42] prospectively compared 20 patients who received a continuous elemental diet infusion during the night time and a low-fat diet during the daytime with 20 patients who received neither nutritional therapy nor food restriction. On an intention-to-treat basis, 5 patients (25%) in the enteral nutrition group and 13 (65%) in the nonenteral nutrition group had a clinical relapse during the 1-year observation ($p=0.03$). At 12 months, endoscopic inflammatory scores were significantly higher in the nonenteral nutrition group than in the enteral nutrition group ($p=0.04$).

In a retrospective cohort study of paediatric patients with CD, Duncan and colleagues[43] described that maintenance treatment with enteral nutrition seemed to be a useful strategy. Out of 48 patients who achieved clinical remission after an 8-week course of EEN, 15 (31%) patients were able to continue partial enteral nutrition, and remission rates at 1 year were 60% (9/15) in patients continuing partial enteral nutrition compared with 15% (2/13) in patients taking

no treatment ($p = 0.001$) and 65% (13/20) in patients taking azathioprine ($p = 0.14$). The GETAID pédiatrique in France recently completed a prospective randomized controlled trial (ClinicalTrials.gov identifier: NCT02201693) on 100 newly diagnosed children/adolescents with CD to maintain clinical remission over 12 months by either cyclic EEN (for 2 weeks every 8 weeks) or partial enteral nutrition with a 25% caloric supplementation by MODULEN IBD. Inclusions are completed and the final results of the study are expected for end of 2019.

Oral diets and IBD

Many different types of diets have been proposed in the treatment of IBD. They are all based on the exclusion of some dietary components. Intense research is ongoing to improve nutritional approaches given the limitation of EEN due to its exclusivity character not allowing any additional food. The study of Johnson and colleagues[44] confirmed that partial enteral nutrition (allowing an unrestricted free diet up to 50% of daily caloric intake) is not effective in inducing complete remission in CD. However, the recent innovative approach of Rotem Sigall-Boneh and Professor Arie Levine offers a very promising alternative to strict EEN. This new diet, called the CD exclusion diet **(CDED)** is based on the idea of excluding potentially 'harmful' or proinflammatory food ingredients. The first report in 2014 showed a high potential to induce clinical remission when combining enteral nutrition with the CDED[45]: all patients received one half of calories from enteral nutrition and one half from an exclusion diet avoiding gluten, dairy products, gluten-free baked goods and breads, animal fat, processed meats, products containing emulsifiers, canned goods, and all packaged products. Clinical remission was obtained in 33 of 47 (70%) of children/adolescents/young adults and normalization of C-reactive protein occurred in 21 of 30 (70%) patients in remission. In this study, seven patients were included who did not take any formula, but followed CDED and six of seven achieved clinical remission with the solid food diet alone. This raises the question of whether the supplementary milk formula is indispensable; it seems rather that it serves as a guarantee for a balanced diet, avoiding deficiencies. A subsequent clinical trial randomizing $n = 78$ patients to EEN or partial enteral nutrition plus CDED showed a comparable efficacy with 30/40 patients in remission at week 6 receiving CDED *versus* 20/34 receiving EEN ($p = 0.38$). While efficacy was similar, tolerance was higher in the CDED group.[46] So far, no data on mucosal healing with CDED are reported, but studies with follow-up endoscopy in patients on CDED are underway. The first data of Professor Arie Levine's studies on CDED indicate that patients coming into remission on CDED induction therapy stay in prolonged remission while following phase II and III of the exclusion diet. Thus, there are clear indicators to believe that enteral nutritional therapy might also play a significant role as maintenance therapy for CD. The initial preliminary analyses of Professor Levine's group indicate that there is a clear difference in the modulation of the intestinal microbiota in patients coming into and maintaining remission on CDED compared with those failing remission.[46]

A somewhat different approach for inducing remission in patients with CD by the sole use of diet was recently reported by the Scottish group led by Professor Richard Russell with a diet called **CD-TREAT**.[47] This diet is based on an idea to mimic, with solid food, the composition and effects of enteral nutrition, particularly on the intestinal microbiota. In a first step, the authors compared the effect of CD-TREAT with EEN on the microbial composition and function (including short-chain acid and sulphite production) in healthy adult volunteers. A total of 25 healthy volunteers were randomized to receive EEN or CD-TREAT first and after a 2-week washout they were crossed over to the other treatment arm allowing individual comparison of changes in faecal microbiota and metabolome. As excepted, tolerance of CD-TREAT was superior to EEN, but the effects on gut microbiota composition and metabolic functions were comparable, encouraging the team after obtaining animal data confirming the anti-inflammatory potential of CD-TREAT to propose it to five children with active CD. After a course of 8 weeks, four of five children responded to CD-TREAT, with three children achieving clinical remission. Only one patient normalized faecal calprotectin on CD-TREAT, the four other children showed a decrease from a mean 1960 ± 1104 mg/kg at baseline to a mean 1042 ± 776 mg/kg at 8 weeks.

One of the most studied exclusion diets for the treatment of IBD is the Specific Carbohydrate Diet **(SCD)**. Initially, it was developed for the

treatment of coeliac disease,[48] but it became very popular in IBD due to several impressive lay reports indicating the potential to treat various diseases, including UC. The principle of the SCD is to remove grains including wheat, barley, corn, and rice; added sugar is limited to honey and also most milk products are restricted except for fully fermented yogurts. The rationale of the SCD is based on the notion that polysaccharides and complex sugars are poorly absorbed in the intestinal tract causing potentially bacterial (and possibly fungal) overgrowth with subsequent inflammation of the intestinal and colonic mucosa. Suskind and colleagues reported clinical remission in seven children with CD after a SCD diet of several months (average 14.6 ± 10.8 months) with a significant improvement of inflammatory markers.[49] An additional retrospective study of the same group[50] confirmed in 20 children with CD and 6 children with UC a marked reduction in disease activity scores under SCD, in line with the observation of 50 adult patients with IBD responding favourably to prolonged SCD. These data were obtained by a patient reported 3-day dietary survey.[51] Cohen and colleagues[52] reported that 8 of 10 children/adolescents with CD responded to a 12-week cycle with SCD; 1 was not able to take the diet, while 1 patient with colonic CD experienced a relapse. In the following study, seven patients continued the diet for 52 weeks. Since these first observations, several studies have been performed, analysing the potential of SCD to control inflammation in children and adults with IBD. Suskind and colleagues[53] showed, in a prospective study on 12 children with mild to moderate IBD (CD and UC), that the addition of SCD over a 12-week period to ongoing medication allowed remission to be reached in 8 of 12 patients; 2 patients did not respond to SCD and two patients were not able to maintain the diet. Microbial analyses of these patients confirmed a marked difference between baseline and after 12 weeks of SCD. Additional retrospective, studies on CD and UC, including one online survey, confirmed the perception of a clinical benefit and the potential of SCD to reduce inflammation and its efficacy inducing and maintaining remission over several months.[50,54,55] While weight loss is a concern when utilizing SCD, many academic IBD centres have developed active dietary programs supporting patients on SCD.[50,51,56] In the study of Cohen and colleagues,[52] repeat endoscopic evaluations were available, indicating the potential of SCD to induce mucosal healing, as shown for two patients and also in the report by Miller and colleagues.[57] Another study[58] failed to demonstrate achieving mucosal healing despite a positive clinical evolution in patients on a modified SCD (integrating some initially excluded foods, such as potatoes, rice, quinoa or oats). Since adherence to SCD, as to other exclusion diets, can be a challenge and modification of SCD might compromise the clinical anti-inflammatory effects, well-designed and precise prospective randomized trials are needed to further affirm this promising treatment option.

The **Palaeolithic diet**[59] is based on the idea that the human intestinal tract is not sufficiently evolved to digest food from modern agriculture and thus, the exposure to foods not present at the time of human evolution may cause modern diseases, such as IBD. In common with other diets, the Palaeolithic diet excludes many food ingredients and privileges the intake of lean, nondomesticated meats and noncereal plant-based foods (i.e. fruits, roots, legumes, and nuts). So far, no data exist on the role of the Palaeolithic diet in the treatment of IBD, except of rare and isolated rather positive case reports.

With time, up to one third of patients with IBD will develop functional gastrointestinal symptoms, sharing similarities with those of irritable bowel syndrome.[60] With the development of better strategies to deal with functional symptoms in patients with IBS, some were extrapolated to patients with IBD. An important strategy to improve symptoms is diet. The most common diet used for IBS is a **gluten-free diet**. This diet may be associated with a better digestive wellbeing according to patients but controlled trials are missing to conclude on the usefulness of this restrictive diet. The second diet used successfully for patients with IBS is a **low-FODMAP** (Fermentable Oligo-, Di-, Mono-saccharides And Polyols) diet. The diet is based on the reduced intake of indigestible and slowly absorbed carbohydrates that may induce symptoms through luminal distension and mechanoreceptor stimulation by virtue of their osmotic effects and fermentation. This is the basis for the lactose-reduced diet in patients with lactose malabsorption and the low-FODMAP diet, in which all short-chain carbohydrates are reduced. The recent prospective study of Cox and colleagues[61] demonstrated that patients with quiescent IBD

scored higher for quality-of-life scores while on a low-FODMAP diet than patients on a control diet, whereas the IBS scores did not significantly differ in the same study. In the same line, the study of Halmos and colleagues[62] showed no effect of reducing inflammatory parameters on a low-FODMAP diet. A recent meta-analysis[63] is largely supportive that a low-FODMAP diet is beneficial for reducing gastrointestinal symptoms in patients with quiescent IBD; there was a significant improvement in symptoms like diarrhoea, abdominal bloating, abdominal, fatigue and nausea. However, a major drawback for patients with IBD might be a potential reduction of the abundance of anti-inflammatory bacteria and thus the risk of aggravating dysbiosis on a prolonged low-FODMAP diet.[61,62]

A short pilot study reported symptomatic improvement through excluding foods with high immunoglobulin (Ig)G4 levels (mostly eggs and beef).[64]

A **semi-vegetarian diet** (lacto-ovo-vegetarian diet) has been shown to maintain a longer clinical remission in patients with CD compared with an omnivorous diet with a remission rate at 2 years of 94% *versus* 33%.[65] This highlights the role for 'good' fibres in the diet in order to enrich the microbiota by giving prebiotics and substrates to protective bacteria. Recent studies have demonstrated that a diet high in fibre is beneficial to both patients with UC and CD.[66,67]

Other dietary interventions?

Diet enriched in omega 3 fatty acid. A Cochrane systematic review has analysed six studies (1039 patients) of omega-3 fatty acid supplementation[68]. There was a marginal significant benefit of n-3 therapy on maintenance of remission. A total of 39% of patients in the n-3 group had relapsed by 12 months compared with 47% of patients on placebo [six studies, 1039 patients; risk ratio (RR) 0.77, 95% confidence interval (CI) 0.61–0.98]. However, when the two largest studies at low risk of bias were considered alone, the benefit was no longer statistically significant (two studies, 738 patients; RR 0.88, 95% CI 0.74–1.05).

Curcumin supplementation. Hanai and colleagues[69] performed the first randomized clinical trial with curcumin, comparing 43 patients with UC on 5-aminosalicylic acid or Sulfasalazine medication with 2 g curcumin supplementation to 39 patients on placebo. Relapse rates at 6 months were 4.6% *versus* 20.5% ($p = 0.049$) favouring curcumin supplementation. However, the recent systematic meta-analysis of Grammatikopoulou and colleagues,[70] based on three randomized controlled trials, could not confirm a significant effect of curcumin on inducing remission in patients with UC compared with placebo. These findings question the role of curcumin as adjunct therapy for IBD.

The results of all of these studies should be interpreted with caution regarding first the small number of patients included in the trials and most often the absence of randomized controlled trials. Secondly, restrictive diets are not without potential adverse effects. In conditions where undernutrition is common in IBD, attention to nutritional adequacy in the face of dietary restriction is essential, and dietetic counselling provided by gastroenterologist or dietician is crucial. Moreover, the effects of reducing carbohydrates with prebiotic actions might have deleterious effects on the gut microbiota. The recent European Society for Clinical Nutrition and Metabolism guidelines on clinical nutrition in IBD did not recommend a specific exclusion diet based on updated literature.[71]

Additional research is clearly needed to answer questions about diet in IBD and to decipher the role of specific diets in the therapeutic management of IBD. However, it is difficult to perform nutritional intervention trials where blinding is very challenging and placebo controls are often impossible. It is also difficult to make unique alterations in the dietary regimen (reducing the proportion of one macronutrient will almost inevitably lead to an increase in another). Many questions remain on the effects of diet and this will be challenging for gastroenterologist in the future.

What clinicians should tell their patients regarding diet

Patient's beliefs on diet

Patients often attribute the clinical symptoms of IBD to their diet. Several studies have provided information on patients' perceptions of symptoms as related to their dietary intake. In a self-reported survey of a large cohort of IBD patients, Cohen and colleagues[72] found that dietary patterns differed

based on IBD subtype and history of surgery, but the foods that were perceived to either worsen or improve symptoms were consistent across all groups. Yogurt and rice were found to improve symptoms within all groups of patients while bananas were found to more frequently improve symptoms in those patients with a total colectomy and an ileal pouch. The foods that worsened symptoms in most groups were as follows: nonleafy vegetables, spicy foods, fruit, nuts, leafy vegetables, fried foods, milk, red meat, soda, popcorn, dairy, alcohol, high-fibre foods, corn-based fatty foods, seeds, coffee, and beans.[72] As expected, patients tended to avoid foods that they reported as worsening their symptoms.

A French study from 2013 looked at dietary beliefs and behaviours in adult patients with IBD.[73] Overall, 15.6% of patients (38/244) believed that diet could cause disease, whereas 57.8% (141/244) believed that food could play a role in relapsing IBD. However, in contrast with the data of Cohen and colleagues,[73] patients in this cohort did not necessarily alter their diet based on their beliefs about diet and its role in IBD flares. For instance, even though 25% of patients believed that dairy products may worsen symptoms during a relapse, only 4% of patients adopted a dairy-free diet during a flare of their disease.

Recommendations for patients

Patients frequently ask physicians for recommendations about food and diet, seeking ways to improve, or even cure their IBD. First, it is important to maintain adequate calorie intake in order to avoid under-nutrition, especially in children and adolescents. Patients with IBD should be checked for micronutrient deficiencies on a regular basis and specific deficits should be appropriately corrected. Second, patients should be counselled to maintain a healthy lifestyle with a healthy diet, well balanced, to stop smoking, do regular exercise and to be regularly supplemented by vitamin D. Third, as discussed herein, there are clear data indicating that exclusion of certain food components is useful for patients with IBD. It seems to be beneficial to exclude industrialized, packed, canned or processed food. In addition, studies indicate that gluten, (possibly some) dairy products, animal fat, and processed meats might amplify the proinflammatory process and some exclusion diets proven to be effective in the first randomized controlled trials. There are various ways to implement these exclusion diets and many studies are planned or are already underway to better understand and define individual diets. For instance, Jowett and colleagues,[74] identified that increased meat consumption, in particular processed meats, and alcohol were associated with a higher risk of relapse in patients with UC, but this was not confirmed in a recent randomized trial in patients with CD.[75] In a prospective, multicentre, observational study of 412 patients with UC in remission during monotherapy with an aminosalicylate, Barnes and colleagues[76] reported that high dietary intake of specific fatty acids, including myristic acid (commonly found in palm oil, coconut oil and dairy fats) was associated with an increased risk of flare.

Consumption of dietary fibre was associated with reduced disease flares in patients with CD but not UC.[77] Recommendations to limit dietary fibre, as proposed in the low-residue diet often prescribed in patients with diarrhoea to enhance digestive comfort should be re-evaluated.

There are no data regarding the use of organic products and the risk of flare. But some recent data suggest that regular consumption of organic food could be protective for the development of some cancers.[78] We can hypothesize that organic food, due to a reduction of pollutants, may reduce the proinflammatory role of food and by this mechanism, help to reduce inflammation in IBD.

Whether diet can be used as a treatment for IBD is a burning question for many of our patients, as is the use of diet to prevent the development and onset of IBD, both in families with already at least one member affected with IBD (high-risk families) or in the general population. Based on the experience with the new exclusion diets, some initial dietetic advice might be recommended. It seems that a certain diet received during childhood and especially adolescence could have a role in developing IBD later in life. The association between diet and risk of IBD seems to exist not only for the current diet just before or at disease onset but there might also be a window of vulnerability during childhood and adolescence.[79] A diet rich in fruits, vegetables and fish between 13 and 17 years of age seems to be protective and the exclusion of industrialized food might become the gold standard in the near future.

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