Review paper

Diet as therapeutic intervention in Crohn's disease

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Abstract

Diet plays an important role in the pathogenesis of inflammatory bowel disease. It has an impact on microbiome, host barrier, and immune response. Clinical studies indicate that various dietary interventions such as exclusive enteral nutrition and exclusion diets might be useful for induction of remission in mild to moderate Crohn's disease, but also for patients failing biological therapy. Current treatment strategies try to solve the problem of poor patient compliance due to the required strict dietary regime. The number of adverse events associated with the use of dietary alternatives is incomparable with the side effects of glucocorticosteroids or biological treatment, which makes them a tempting therapeutic option.

Introduction

Crohn's disease (CD) is an inflammatory bowel disease (IBD), with an increasing prevalence in western countries. Despite the progress in medical technology, CD treatment remains a considerable problem due to individual drugs' susceptibility and associated side effects.

The multifactorial nature of IBD explains the multiplicity and personal approach to every patient in clinical practice. 19–26% of all cases comprise hereditary variance of IBD [1]. The first identified gene related to CD was NOD2 located on chromosome 16. Its mutations lead to disturbance in NOD2 protein synthesis, which activates nuclear factor NF-κB, making it responsive to bacterial lipopolysaccharides [2]. Since the discovery of the first CD gene in 2001, over 200 other genetic loci responsible for the disease's subphenotypes and treatment response have been described [1].

Current data indicate an increase in the significance of environmental factors in the pathogenesis of CD [3]. In healthy individuals, intestinal epithelium acts as a barrier preventing the entry of foreign antigens, toxins, and microorganism from the lumen of the epithelium. It consists of a mucous layer, epithelial cells, and tight junctions between the cells. The colon mucous should be impenetrable to bacteria. In animal models that spontaneously develop colitis, bacteria can penetrate the mucinous layer, reach the epithelium, and activate an immune response [4]. In a study performed by Kleessen *et al*., bacterial mucosal invasion was present in 55.6% of the ileal and in 25% of the colonic specimens from CD patients. No bacteria were detected in the tissues of the controls [5].

Intestinal bacteria are thought to be involved in the inflammatory process. Both the composition of the intestinal microbiota and bacteria translocation are found to be significant in the pathogenesis of IBD [6]. Microbiome studies have linked intestinal dysbiosis, understood as microbiota's imbalance of composition and function, with IBD susceptibility. Research indicates that it is the loss of beneficial microorganisms (i.e. *Faecalibacterium, Christensenellaceae, Methanobrevibacter, and Oscillospira*), rather than the gain of more pathogenic bacteria (*i.e. Fuscobacterium* and *Escherichia*), that is responsible for intestinal inflammation [7].

One of the key players in normal gut microenvironment is diet. It has an impact on the microbiome, host barrier, and immune response. Several studies indicate that low fibre intake, a high-fat and high-sugar diet, exposure to gluten, amylase, and trypsin inhibitors in

wheat and food additives affect host immunity and microbiome via multiple pathways [8].

The health benefits of consuming dietary fibre are well known and accepted worldwide. Non-digestible polysaccharides are significant for butyrate and short-chain fatty acid (SCFA) synthesis. Butyrate suppresses cytokine production and induces regulatory T (Treg) cells, which decrease inflammatory and allergic responses [9]. In animal models soluble fibres and resistant starch decrease interferon γ (IFN-γ) production by CD4+ T-cells and increase the cytokine synthesis inhibitory factor (IL-10) level, which consequently suppresses gut inflammation [10]. Desai *et al*. proved that during chronic or intermittent dietary fibre deficiency, the gut microbiota absorbs host mucous glycoproteins as a nutrient source, leading to erosion of the colonic mucus barrier [11].

The western diet is characterised by exposure to high-fat and high-sugar (HF/HS) food ingredients. In the study conducted by Martinez-Medina *et al*., an HF/HS diet led to dysbiosis in transgenic mice, which resulted in a decrease in mucus layer thickness and increased intestinal permeability. Furthermore, the HF/HS diet caused TNFα induction and decreased MUC2 gene expression, encoding mucin protein [12]. Other studies indicate a negative impact of HF/HS on butyrate and SCFA synthesis [13]. The HF diet is also proven to increase IFN-γ expression and decrease levels of Treg cells [14].

To improve the taste and appearance of consumed meals, the western diet is enriched with food additives, such as emulsifiers, thickeners, and sweeteners. One of them is carrageenan (E407), used in the food industry for stabilizing suspensions and emulsions such as sauces, jams, and dairy products. Recent studies suggest that carrageenan affects gut epithelial structure and function by redistribution of the tight-junction protein zonula occludens, changes in cellular F-actin architecture, and increased permeability to the transfer of macromolecules [15]. Other components of processed food, like carboxymethylcellulose (CMC) and polysorbate-80 (P80), increase the proinflammatory potential of human microbiota [16], promote bacterial translocation across the epithelium, trigger bacterial adherence, and generate mucus erosion [17]. Thickeners and sweeteners (e.g. maltodextrins) enhance the intestinal immune response by increased production of IgA in the intestinal mucosa [18].

Not only additives cause intestinal imbalance. Exposure to wheat ingredients like gluten and amylase-trypsin inhibitors (ATIs) promote an inflammatory state. ATIs are promotors of immune response via activation of the toll-like receptor 4 (TLR4) on myeloid cells [19]. It is well known that gluten decreases the concentration of Treg cells [20], reduces occludin expression [21], and induces zonulin release (both are tight junction membrane proteins) [22]. It is also responsible for IL-10 increase [23].

Considering the data mentioned above and the multifactorial nature of inflammatory bowel disease, it is logical to suppose that dietary intervention itself can be an effective form of therapy, which will be presented in the following paragraphs.

Diet in Crohn's disease

In CD dietary treatment is an effective method to induce or maintain remission and relieve symptoms of the primary disease. It is useful to determine which of the widespread dietary interventions have convincing evidence for recommendation (Table I).

Exclusion diets have long been tested for their utility in the treatment of CD. Popular, but not entirely effective, is the gluten-free diet (GFD). Although gluten has been proved as a pro-inflammatory agent, there have been no prospective studies evaluating the role of GFD in the induction and maintenance of remission in IBD. Data from a recent meta-analysis suggest that GFD may improve symptoms in IBD, but due to a lack of high-quality evidence, the universal use of GFD in IBD cannot be supported [24].

Plant-based diets (PBD) are listed as healthy eating patterns and are recommended by the U.S. Department of Health and Human Services. There is, however, little evidence to prove its effectiveness in inducing and maintaining remission in IBD. A prospective, single-centre, clinical trial conducted in Japan by Chiba *et al.* included 22 adult CD patients who achieved clinical remission and consumed PBD during hospitalization. They were advised to continue the diet and avoid high-risk foods for IBD for 2 years. Seventy-three percent of the participants followed the instructions given. Remission was maintained in 15 of 16 patients (94%) vs. 2 of 6 in the controls (33%) in 2-year follow-up [25]. It is difficult to determine whether it was the avoidance of high-risk food and meat or the presence of fruits and vegetables that was responsible for the outcome of the study. Larger controlled trials are needed to validate these results.

As with the diets listed above, the low-FODMAP diet (LFD) is not sufficiently tested to be effective in IBD treatment. Reports indicate potential efficacy in relieving IBS-like symptoms experienced by IBD patients [26, 27]. Cox *et al.* showed that a 4-week diet low in fermenting saccharides reduces the intensity of some intestinal symptoms in IBD patients and improves the quality of life [28]. Thus, LFD should be a viable option in these cases.

Undernutrition is common in IBD, so the use of restrictive diets should be supervised by a dietician.

Table I. The role of dietary factors in the pathogenesis of Crohn's disease

Dietary component	Effect
Fibre	• Fibre increases butyrate and short-chain fatty acid (SCFA) synthesis • Butyrate suppresses cytokine production and induces regulatory T (Treg) cells • Soluble fibres and resistant starch decrease IFN-γ production by CD4+ T-cells and increase cytokine synthesis inhibitory factor (IL-10) • Chronic or intermittent dietary fibre deficiency leads to erosion of the colonic mucus barrier
High-fat and high-sugar diet	• Dysbiosis in transgenic mice • TNF-α induction and decreased MUC2 gene expression • Negative impact on butyrate and SCFA synthesis • Increased IFN-γ expression and decreased levels of Treg cells (HF)
Carrageenan (E407)	• Redistribution of the tight-junction protein zonula occludens • Changes in cellular F-actin architecture • Increased permeability to the transfer of macromolecules
Carboxymethylcellulose (CMC) and polysorbate-80 (P80)	• Increased proinflammatory potential of human microbiota • Bacterial translocation across epithelium • Increased bacterial adherence • Mucus erosion
Thickeners and sweeteners	• Increased production of IgA in the intestinal mucosa
Amylase-trypsin inhibitors (ATIs)	• Promotors of immune response via activation of the toll-like receptor 4 (TLR4) on myeloid cells
Gluten	• Decreased concentration of Treg cells • Reduced occludin expression • Zonulin release • IL-10 increase

Exclusive enteral nutrition

The current consensus guidelines of ECCO/ESPGHAN on the management of paediatric CD recommend the use of exclusive enteral nutrition (EEN) as first-line treatment to induce remission in new onset mild to moderate CD in children. The basic assumption of this method is a supply of whole-protein formula for 6–8 weeks as the only source of nutrition. The formula should be applied orally or through a nasogastric tube in the case of failure to provide adequate oral intake. Whole-protein formula can be replaced with elemental formula in children with special medical indications like cow's milk allergy. The clinical response should be observed within 2 weeks. After the treatment, a gradual re-introduction of food with decrease of formula is suggested for the next 14–21 days [27, 29]. EEN is a well-documented method of treatment. Its effectiveness in obtaining clinical remission is approximately 80% [30–32]. There is no difference in efficacy between EEN and corticosteroid therapy [33]. The potential adverse events associated with EEN are diarrhoea, constipation, nausea, abdominal pain, bloating, and taste fatigue [34]. Usually, they are temporary and pass with time. The only severe life-threating event is refeeding syndrome observed in patients with severe malnutrition, but it can be avoided with careful laboratory monitoring [35, 36]. Well-known side-effects of corticosteroids and minimal on-diet risk make enteral nutrition a better choice for therapy. EEN helps not only to eliminate all the negative effects of steroids, but also prevents malnutrition, associated with inadequate bone mineral density, growth, and puberty disorders [37, 38].

Beneficial results obtained in the paediatric population encourage the use of EEN in adults. However, in a review by Wall *et al.* the effects of such treatment are diversified [39]. Although remission was achieved in similar percentage of patients who completed the treatment with EEN or corticosteroids (CS) – 27–100% for EEN and 30–100% for CS, respectively – the number of participants who did not complete EEN intervention was up to 50% depending on the study [38]. The poor compliance resulted from unpalatable formula, lack of support, and poor motivation to follow the treatment guidelines [40, 41].

It is also a subject of discussion whether EEN is more effective in new onset CD than in patients with existing CD. This appears to be the general trend of any therapy used in CD. For example, the response and remission rates achieved with biologic therapy in children are greater than in adults [42]. This may be due to complications that occur with time in CD patients, such as abscesses, strictures, and fistulas, the treatment of which becomes more challenging. However, recent reports illustrate a beneficial role of EEN in penetrating and stricturing CD both in children and adults [43].

Based on the present data, the use of EEN as a treatment option should be available for a selected group of adults – especially for motivated ones who are willing to adhere to the high dietary requirements of EEN.

Partial enteral nutrition

EEN can be challenging for patients. To minimize negative experiences, the idea of partial enteral nutrition (PEN) with whole-food consumption was developed. It is based on the supply of liquid formula with free access to an unrestricted diet. The first randomized controlled trial on PEN was published in 2006 by Johnson *et al.* In this study 50 children with active CD were randomly assigned to either the PEN or EEN group. For 6 weeks patients in the PEN group obtained 50% of calories from liquid formula and 50% from an unrestricted diet. The statistical analysis of the survey's data showed that EEN was associated with a significantly higher remission rate than PEN (42% vs. 15%). Moreover, EEN treatment resulted in an increase in haemoglobin and serum albumin concentration and reduction in platelet count and ESR. No such changes were observed with PEN therapy [44].

Gupta *et al.* developed a new PEN protocol in which patients received 80 to 90% of their caloric needs from liquid formula with an opportunity to consume the remaining calories from a normal diet. Remission was achieved in 65% of participants, and the response rate was 87% [45]. Considering the 80% remission with EEN [30–32], the proposed PEN protocol seems to be a promising therapeutic option. Furthermore, changes in laboratory parameters demonstrated the effectiveness of the following method in reducing inflammatory marker levels – ESR and CRP. The described increase in albumin concentration reflected the proper nutritional status of the patients.

Summarizing, PEN could be more acceptable and better tolerated by patients, which would translate to better treatment compliance. However, current data do not justify recommendation of PEN in general use and further studies must be conducted to support this matter.

Crohn's disease exclusion diet

Partial enteral nutrition (PEN) with exposure to any available food is not entirely effective in inducting remission and reducing inflammation in CD patients [44]. At the same time, exclusive enteral nutrition (EEN) with complete avoidance of regular food has an established position in IBD treatment and is widely recommended as first-line therapy in mild to moderate CD [28]. Population studies among families of CD children have shown that the use of solid food-based diets is the preferred alternative to EEN for paediatric patients and their parents [46]. The absence of palatable meals with intake of high amounts of liquid formula requires great commitment from patients and creates a compliance problem, which is more visible in adults.

To improve patients' satisfaction, attempts have been made to introduce diets based on generally available foods, which would be as effective as EEN in achieving and maintaining remission in CD patients. Because PEN with free-diet-exposure is not entirely effective, it was suspected that avoidance of dietary ingredients with a pro-inflammatory effect, not the use of enteral nutrition itself, is responsible for the better outcome of EEN [47].

Based on the assumptions above, Prof. Arie Levine created the Crohn's Disease Exclusion Diet (CDED with PEN or CDED alone) to fulfil the needs of patients who had difficulty in continuing EEN despite an initial clinical response [48]. Eventually, for patients with mild to moderate CD who were not willing to undergo EEN, it became a standard practice in the Professor's clinic.

For induction of remission, the described dietary intervention was divided into 2 phases, each lasting for 6 weeks (12 weeks in total). The first period was the most restricted one. 50% of daily calories were supplied with polymeric formula. Although the patients were advised to consume the formula, individuals who refused to drink it could take the diet without supplementation. The other Fifty percent of calories came from the mandatory food: minimum 150–200 g of chicken breast a day, 2 eggs a day, 2 fresh, peeled, and cooked potatoes a day, 2 bananas a day, and 1 apple a day. There were also other allowed foods and beverages, which enriched the daily diet with different taste experiences. The presence of products with proven absence of a negative effect on intestinal mucosa was supposed to improve adherence to dietary recommendations. In the second phase, the list of allowed ingredients was more varied. At the same time, the volume of consumed formula was reduced to 25% of the daily caloric demand. The basic intention was to avoid products with proven pro-inflammatory status.

The first results from 47 patients (34 children, 13 adults) reported effectiveness of CDED at the level of 78.7% in terms of clinical response and 70.6% in terms of clinical remission by week 6. It was accompanied by a significant decrease in CRP and ESR levels. Moreover, 6 out of 7 patients who used CDED without polymeric formula supplementation entered full remission [48].

A study conducted several years later compared the effectiveness of EEN vs. CDED + PEN in paediatric patients [49]. The tolerance of CDED + PEN was significantly higher than that of EEN (97.5% vs. 73.7%,

respectively, $p = 0.002$). No statistical differences were observed in achieving clinical response (85.0% for CDED + PEN vs. 85.3% for EEN, $p = 0.97$) and obtaining remission (75% vs. 58.8%, respectively, $p = 0.14$). By week 6 the calprotectin level dropped in both groups ($p = 0.002$). The L/M ratio, which reflects intestinal permeability, did not differ significantly. After 6 weeks, EEN patients started to gradually return to a free diet. At the end of week 12 maintenance of remission and normal CRP was significantly higher in the CDED + PEN group. From week 6 the calprotectin level in EEN group started to increase. Moreover, the microbiome changes induced by EEN in the first 6 weeks started to revert, probably due to exposure to a normal diet. However, this was not observed in CDED + PEN participants.

CDED has proven to be effective for induction of remission in patients failing biological treatment [50]. In a retrospective analysis of 21 patients using dietary therapy for loss of response to biologics, remission was obtained in 62% of cases. Improvement in previously elevated inflammatory markers occurred in 81% of patients, and normalization in 40.9%. Regarding the location, the highest remission rate was achieved in the isolated ileal disease – 83.3%, while compliance was at the level of 81%. The study pointed out that dietary therapy could be considered in patients who are difficult to treat.

Reduced exposure to dietary components that have adverse effects on the microbiome and intestinal barrier is a simple but effective method of treatment for CD patients. The obtained results explain the increasing use of CDED in clinical practice.

Parenteral nutrition

Parenteral nutrition (PN) is indicated in patients with inflammatory bowel disease when oral or enteral nutrition is inadequate or impossible. The absolute indication for total parenteral nutrition is obstruction of the gastrointestinal tract, making it impossible to place a feeding tube behind it. PN is also used in patients with short bowel syndrome (malabsorption of nutrients, loss of fluids and electrolytes), in patients who do not tolerate enteral nutrition (before that, analyse if the diet, speed flow of the liquid formula, and the position of tube are optimal). When enteral nutrition is insufficient (e.g. it does not cover the full demand for nutrients, electrolytes, fluids), it is advised that enteral nutrition be combined with parenteral nutrition (supplementary PN) [27, 51, 52].

Nutritional intervention in the form of parenteral nutrition should be limited to patients who strictly require it, because this form of treatment is associated with complications such as infections and refeeding syndrome. Refeeding syndrome is a complication that is rare in patients treated appropriately; however, attention should be paid to the supply of phosphate and thiamine in patients at risk of occurrence [53].

The use of immunomodulating ingredients such as glutamine in parenteral nutrition is currently not recommended. A review from 2021 described the lack of influence of glutamine on anthropometric measurements, the course of the disease, or markers of inflammation in patients with IBD [54].

Summary

The aetiology of CDe is complicated and not fully understood. Current scientific data indicate a significant role of diet in modulating the immunological response in the intestinal mucosa. Therefore, it is important to find an effective dietary intervention for CD patients with a relatively acceptable dietary regime. The Crohn's Disease Exclusion Diet (CDED) in combination with PEN is a promising therapeutic intervention that allows high compliance to be maintained thanks to acceptable requirements without losing the therapeutic effect. The number of adverse events associated with the use of dietary alternatives is incomparable with the side effects of GCS or biological treatment, which makes them a tempting therapeutic option.

Conflict of interest

The authors declare no conflict of interest.

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