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EDITORIAL

Dietary interventions in Crohn's disease: A simple solution to refractory disease

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Crohn's disease (CD) is an inflammatory condition of the gastrointestinal tract with a multi-factorial etiology. The interaction of environmental factors in genetically predisposed individuals contributes to the pathogenesis of CD. The emergence of the disease paralleling the western lifestyle has put focus on the western diet as an inciting factor in the development of CD [1]. With diet being established as an inciting agent, treatment options focused on eliminating these inciting factors aside from the regular immunosuppressive agents. Diets such as exclusive enteral nutrition (EEN), Crohn's disease exclusion diet (CDED) plus partial enteral nutrition (PEN) and specific carbohydrate diet started gaining significance [1, 2].

In the current issue of the *Indian Journal of Gastroenterology*, Arcucci et al. [3] conducted a randomized control trial in 21 children of CD on biologicals (infliximab, adalimumab or vedolizumab), who were asymptomatic but had an elevation of fecal calprotectin. Dietary intervention was used as an add-on therapy to the ongoing biological therapy for a period of 12 weeks. Eleven children were randomized to the CDED + PEN group and 10 to regular diet (RD) group. In the first six weeks, patients in the CDED + PEN were allowed to meet 50% of their nutritional requirements through the permitted solid food (CDED) and the rest 50% through polymeric formula (Modulen-IBD, Nestle Health Services, Switzerland), while in the next six weeks 75% of their nutritional requirement was met by the CDED and remaining 25% by the formula. Patients in the RD arm were allowed to eat ad-libitum and also had consultation with a dietician regarding a healthy diet. Patients on CDED + PEN had a greater reduction in their fecal calprotectin levels (> 50% reduction from baseline in 9/11 of CDED + PEN arm vs. 2/11 in RD arm, $p = 0.005$) and lesser need for dose intensification of their biologicals (1/11 in CDED + PEN vs. 8/10 in RD group, $p = 0.005$). Frequency or dose of biologicals were reduced in 2/11 children in the CDED + PEN group and none in the RD group. However, there was no difference in patients having a relapse on follow-up (1/11 in CDED + PEN vs. 4/10 in the RD group, $p = 0.149$). They did not report any issues in the compliance with CDED + PEN. A few concerns with the study include lack of levels of biological agents or their antibodies (due to issues of availability and affordability), whether disease duration was matched for patients in both groups, to what extent advice regarding healthy diet modified the dietary pattern in patients of the RD arm, short-term follow-up and small sample size. Nevertheless, this study highlights the importance of diet in patients with CD not just for growth, but also as a therapeutic agent in their management.

Dietary factors in the pathogenesis of Crohn's disease

Various epidemiological studies tried to identify the dietary factors responsible for inflammatory bowel disease (IBD). The European Investigation Into Cancer and Nutrition (EPIC) study found that greater consumption of linoleic acid as found in red meat, margarine and cooking oils was associated with a greater risk of developing ulcerative colitis (UC) [4]. Similarly, in the Nurses' Health Study, the consumption of large amounts of fiber was associated with a lesser risk of developing CD subsequently [5]. Gut microbiota plays an important role in the pathogenesis of IBD with dysbiosis in the form of reduced *Firmicutes* and increased Enterobacteriaceae were seen [6]. Diet is known to have a

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significant effect on gut microbiota. Subsequently, the influence of western diet to the development of CD was studied in various animal models. Devkota et al. used IL10-/- mice and gave three different diets to them: low fat (LF), polyunsaturated fatty acid (PUFA) and milk derived fat (MF). They reported a lower diversity of microbiome in mice receiving PUFA and MF diet and an increased ratio of Bacteroidetes to *Firmicutes* in them. Interestingly, the incidence of colitis was higher in the mice receiving MF diet and this was attributed to a pro-inflammatory bacterium *Bilophila wadsworthia* seen only in the mice receiving this diet. MF diet induces the production of taurine conjugated bile acid which are rich in sulfur that is required for the growth of *B. wadsworthia*, predisposing them to develop colitis [7]. Western diet is known to contain preservatives and emulsifiers that are also implicated as causative factors in the pathogenesis of IBD. Carboxymethyl cellulose (CMC) is a preservative commonly found in dairy products and bread. Mice that were given 2% CMC solution had bacterial overgrowth 30,000-fold higher than control mice [8]. Artificial sweeteners such as saccharin caused dysbiosis in mice. Red 40 (E129) and Yellow 6 (E110), food colorants, caused colitis in mouse models [1]. Carrageenan a sulfated polysaccharide used as a stabilizer in dairy and meat products, increased intestinal permeability in cell cultures [9].

Dietary interventions in Crohn's disease

With the findings of the above studies, multiple dietary interventions came into effect to avoid the excessive intake of certain food stuffs and completely avoiding some. These were postulated to reduce the dysbiosis and inflammation of bowel in patients with IBD. These dietary strategies also aim at improving the nutritional status of patients, as it is an important determinant of the outcome of such patients.

Exclusive enteral nutrition (EEN) is a nutritional strategy that provides the total nutritional requirement of the patients through a liquid formula for a period of six to eight weeks [2, 10]. This formula may be elemental, semi-elemental or polymeric. There is no difference in their efficacy. However, palatability is better with polymeric formula and therefore likely to have better compliance. EEN improves the nutritional status of the patient and provides an anti-inflammatory effect. These formulas are devoid of lactose, gluten and fiber. The anti-inflammatory effect of EEN is derived from the avoidance of dietary antigens and deactivation of intra-cellular signaling pathways such as NF-kB and restoration of cell-to-cell adhesion molecules. Arginine and lysine are the two amino acids responsible for the deactivation of inflammatory signaling pathways [2]. The microbiome of the children who responded to EEN was found to be different from those who did not [11, 12]. Future responders may be identified. EEN has been found to be more effective than corticosteroids and as effective as biologicals for the induction of remission (in up to 86% patients) [13, 14]. The continuation of EEN for a prolonged period of time as maintenance therapy is impractical. Therefore, maintenance enteral nutrition to meet at least 25% of the nutritional requirement by formula and the rest by normal diet was considered. However, results were not satisfying [15–17]. EEN as maintenance therapy (in a different protocol) along with other immunosuppressive agents was tried (given for month-month duration at four monthly intervals over one year). Even though corticosteroid requirements were lower, these trials were not replicated with a larger number of participants [18, 19]. Therefore, EEN is not recommended for the maintenance of remission [10]. Gradual reintroduction of food items to return to a normal diet is generally preferred. In the pre-surgical setting, EEN has improved the post-operative outcome of patients such as decreased post-surgical hospital stay [20]. Studies have shown a significant improvement in the lean body mass, fat free mass and bone mineral density in children with CD on EEN [21]. Initially, EEN was considered to be more effective in patients with ileal involvement [22]. However, subsequent studies have shown no difference in efficacy based on the location of disease [23].

Crohn's disease exclusion diet (CDED) eliminates potential food allergens. Compliance to EEN is its major setback as a strict commitment to only a single liquid diet is needed. Hence, diets that allowed solid foods such as CDED started gaining importance. Gluten, dairy products, animal fat, red meat, emulsifiers, maltodextrins and carrageenan are excluded from the diet. This dietary intervention is in two stages: stage 1: 50% of the nutritional requirement is provided by the exclusion diet and the remaining 50% by a propriety formula (PEN) for six weeks. Stage 2: the formula accounts for only 25% of the nutritional requirement and remaining 75% being met by the exclusion diet that progressively becomes more liberal, but still avoides the main allergens [2, 24]. It was found to be effective and better tolerated than EEN [23]. CDED + PEN has also been used as a maintenance diet. Yanai et al. showed that 50% of patients on CDED alone or with PEN (no other immunomodulators) achieved sustained clinical remission and 35% of them achieved endoscopic remission [25].

Crohn's disease treatment with eating (CD-TREAT) is a food-based therapy individualized to each patient. The composition of EEN is recreated as closely as possible by excluding dietary components such as gluten and lactose [26].

Specific carbohydrate diet (SCD) is a grain-free diet proposed as a maintenance diet in patients with IBD. The diet allows monosaccharide carbohydrates contained in fruits,

Table 1 Summary of efficacy of dietary interventions in children with Crohn's disease

Authors	Study design	Study details	Study findings
Cohen-Dolev et al. ($n=147$) [33]	Prospective study in newly diagnosed CD	EEN ($n=60$) vs. corticosteroids ($n=87$) EEN: 6–8 weeks	Remission rates were better in EEN (63% vs. 47%, $p=0.036$)
Levine et al. ($n=78$) [24]	RCT in CD diagnosed within 36 weeks of study	EEN ($n=38$) vs. CDED ($n=40$)	Remission: 58.8% vs. 75%, $p=0.14$ Tolerance: 73.7% vs. 97.5%, $p=0.002$
Grover et al. ($n=34$) [34]	Prospective. Newly diagnosed CD	EEN for 6 weeks	Clinical remission: 84% Biochemical remission: 76% Early good endoscopic response in 58%
Sigall-Boneh et al. ($n=47$) [35]	Retrospective study Children and young adults with CD	CDED + PEN for 12 weeks	Response: 78.7% Remission: 70.2% Reduction in PCDAI: 27.7 ± 9.4 to 5.4 ± 8 ($p<0.001$)
Svolos et al. ($n=5$) [26]	Observational study	CD-TREAT diet for 8 weeks	Clinical response: 80% Remission: 60% Decrease in calprotectin: 80%

CD Crohn's disease, *EEN* exclusive enteral nutrition, *CDED* Crohn's disease exclusion diet, *PEN* partial enteral nutrition, *CD-TREAT* Crohn's disease treatment with eating, *RCT* randomized control trial, *PCDAI* Pediatric Crohn's disease activity index

nuts, eggs and non-starchy vegetables, while restricting grains, corn, milk, cream and artificial sweeteners [27–29].

Anti-inflammatory diet is a modification of SCD, where grain-derived carbohydrates, refined sugars and lactose are restricted. In addition, prebiotics and probiotics are added to the diet [2].

Mediterranean diet (MD) is rich in fruits, vegetables, legumes, cereals, fish and unsaturated fats. Microbiota in the patients on MD were found to have increased beneficial *Prevotella* and *Firmicutes* species. Patients on long-term MD were found to have fewer flares on follow-up [28]. Lewis et al. compared a 12-week SCD vs. MD in adult patients and found that symptomatic remission was seen in around 40% of the patients and neither diet was superior to the other [28].

Low fermentable oligosaccharides disaccharides monosaccharides and polyols diet (LFD) has been shown to improve the symptoms of concomitant irritable bowel syndrome in patients of IBD [30–32].

The efficacy of the above diets in patients with CD has been summarized in Table 1 [24, 26, 33–35].

Traditionally dietary interventions such as EEN and CDED are utilized to induce remission in patients with CD at the time of diagnosis [36]. However, a few studies have reported its use in patients on long-term treatment. Sigall Boneh et al. analyzed 21 patients of CD with a loss of response (LOR) to biologicals. CDED as an add-on to their ongoing medical management induced remission in 62% of them [37]. Similarly, Jijón Andrade et al. reported six patients of CD on biologicals with LOR. CDED + PEN as an add-on therapy resulted in clinical remission in all of them at 12 weeks [38].

Diet and lifestyle contribute significantly to the pathogenesis of CD. Dietary interventions are safe and effective. Even though dietary interventions such as EEN are most effective in treatment naïve patients, these can be considered as an add-on therapy in refractory disease. EEN is the recommended form of dietary intervention at present for the induction of remission in mild to moderate CD [9]. However, CDED + PEN has shown similar efficacy and better tolerability in multiple studies and is likely to play a greater role in future.

Declarations

Ethical approval Not applicable.

Conflict of interest SSV and UP declare no competing interests.

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