DIET IN CROHN DISEASE – THE EFFECT OF DIET ON THE MICROBIOME AND ITS ROLE AS A THERAPEUTIC MODALITY

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Abbreviations

CARD15/NOD2 – Caspase recruitment domain-containing protein 15/nucleotide-binding oligomerization domain-containing protein 2

CD – Crohn disease

CDAI – Crohn disease Activity Index

CDED – Crohn disease Exclusion Diet

CD-TREAT – Crohn disease treatment with eating

CXCL-1 – Chemokine (C-X-C motif) ligand 1

E. coli – Escherichia coli

ECCO – European Crohn's and Colitis Organisation

EEN – Exclusive enteral nutrition

ESPGHAN – European Society of Paediatric Gastroenterology, Hepatology, and Nutrition

F. prausnitzii – Faecalibacterium prausnitzii

FOS – Fructo-oligosaccharides

GI – Gastrointestinal

HBI – Harvey-Bradshaw Index

IBD – Inflammatory bowel disease

IL-6 – Interleukin 6

IL-8 – Interleukin 8

IL-10 – Interleukin 10

NF-κB – Nuclear factor kappa B

PEN – Partial enteral nutrition

RCT – Randomised controlled trial

SCFA – Short-chain fatty acids

SNP – Single nucleotide polymorphism

1. Introduction

Crohn disease (CD) is a chronic inflammatory bowel disease (IBD). The disorder is characterised by relapsing and remitting episodes of inflammation of the gastrointestinal (GI) tract, as well as multiple extraintestinal manifestations and malabsorption. The aetiology and pathophysiology of CD is multifactorial, complex, and not completely known. Thanks to large amounts of well-designed research and studies, multiple pharmacological treatment options for CD exist, which have improved the prognosis significantly. The incidence of CD is higher in Western societies, and the incidence is increasing in developing countries. There are both genetic and environmental risk factors.

It's known that environmental risk factors related to diet and nutrition affects the risk of developing CD. It's also known that the microbiome is altered in CD patients, and that interactions between the microbiome and immune system play a major role in the pathophysiology. Many CD patients report a subjective correlation between certain dietary patterns or food and the risk of relapse. These facts kept in mind, it's logical to expect diet and nutrition to affect the prognosis of the disease as well, possibly by directly affecting the microbiome. This paper will seek to summarise the current scientific data on the role of diet and nutrition in the microbiome and management of Crohn disease.

2. Background

2.1. Clinical features of Crohn disease

Crohn disease is one of the two main manifestations of inflammatory bowel disease, the other being ulcerative colitis (UC). CD is a chronic inflammatory condition characterised by relapsing and remitting episodes of transmural inflammation, as well as "skip lesions", segments of normal-appearing bowel interrupted by areas of disease.[1] Although any part of the GI tract may be involved, the distal ileum and proximal colon are most commonly involved.

The cardinal clinical features of Crohn disease include abdominal pain, diarrhoea, fatigue, and weight loss, but the disease can cause a large variety of symptoms.[2] The abdominal pain frequently has a crampy characteristic, and it's location frequently corresponds to the affected part of the GI tract. With the most frequently affected area being the distal ileum and proximal colon, the abdominal pain is usually located in the right lower quadrant. Bowel symptoms frequently fluctuate and can contain gross blood if the colon is largely affected.

Transmural inflammation may give rise to fistulas, which can cause symptoms on their own, like recurrent urinary tract infections in case of enterovesical fistulas, passage of gas through the vagina in case of enterovaginal fistulas, and excretion of bowel contents to the surface of the skin in case of enterocutaneous fistulas.

Malabsorption frequently contributes to the clinical features of people with small bowel CD. Small bowel inflammation may lead to protein malnutrition, calorie malnutrition, hypocalcaemia, and vitamin deficiency, among others. B12 deficiency is especially characteristic.

Extraintestinal manifestations are not unusual in persons with CD. The most common extraintestinal manifestations include arthritis or arthropathy, eye disorders like uveitis, skin disorders like erythema nodosum and pyoderma gangrenosum, primary sclerosing cholangitis, renal stones, metabolic bone disease, among others.[3] Most of these complications are usually related to the activity of the Crohn disease and therefore occur less frequently in those with well-controlled disease.

2.2. Incidence and prevalence of Crohn disease

IBD, including CD, generally have a higher incidence and prevalence in developed nations and an increasing incidence and prevalence in nations which are becoming increasingly westernized. Within Europe, countries like Norway, Sweden and Hungary have the highest prevalence of CD, at 0,26%, 0,19%, and 0,20%, respectively.[4,5] Croatia and Romania have the lowest prevalence, at 0,0045% and 0,00151%,

respectively.[4] Since the 1990s, most studies on the incidence of Crohn disease and ulcerative colitis in Europe and North America show stable or decreasing incidence. This has been theorized to be the result of decreased exposure to certain environmental risk factors in these areas, like smoking.

The incidence rates for both CD and UC are highest among the second to fourth decades of life.[6] According to one study from Minnesota, USA, the median age of diagnosis for CD was 29,5 years, and the 20-29 age group had the highest incidence rate.[7] Approximately two-thirds of CD cases were diagnosed under the age of 40 years.

2.3. Environmental risk factors for Crohn disease

The aetiology and pathophysiology of IBD is multifactorial, complex, and not completely known. The global incidence of IBD has increased dramatically over the last half-century, which clearly points to the role of environmental factors in the development of IBD.[6] Many environmental risk factors for developing CD are known, including smoking, better living conditions during childhood, not having been breastfed, decreased physical activity, certain medications, certain infections, as well as various dietary factors.[8–12] These dietary factors include decreased intake of dietary fibre, increased dietary intake of total fat, animal fat, polyunsaturated fatty acids, and omega-6 fatty acids, and decreased vitamin D intake.[13,14]

2.4. Genetic risk factors for Crohn disease

More than 85% of CD patients have no family history of IBD[15]. However, twin studies have shown strong clinical evidence of heritable risk factors. The concordance rate for CD for monozygotic twins is 50%[16], showcasing a strong genetic component. Interestingly, the concordance rate for UC is much lower than that of CD, only 19%. Genetic risk factors also confer a risk for certain clinical patterns, including the CD location and type. There is an approximately 49 – 86% concordance of disease site and clinical type of disease in family members with CD.[17,18]

Over 200 single nucleotide polymorphisms (SNPs) are known to be associated with susceptibility to IBD[19], but these polymorphisms confer a modest effect individually. CARD15/NOD2 is located on the IBD1 locus on chromosome 16 and was one of the earliest researched genes involved in CD development. A prospective cohort of 186 children found a prevalence of CARD15/NOD2 mutations in 42% of CD patients.[20] Mutations in this gene confer susceptibility to ileal CD. The CARD15/NOD2 protein activates NF-κB in response to muramyl dipeptide, a fragment of bacterial peptidoglycan[21], highlighting a link between genetic risk, the innate immune system and the microbiome. Other pathways implicated in genetic risk include the autophagy pathway, adaptive immunity, Paneth cell biology, and the ER stress/unfolded protein response.[19,22,23]

2.5. Morbidity and healthcare-associated costs of Crohn disease

IBD causes significant morbidity, and accounts for substantial costs to the health care system and society.[24] Many patients have a continuous and progressive course of active disease, causing significant disability in life. According to a Norwegian population-based ten-year follow-up study, the cumulative relapse rate during the first 10 years after diagnosis was 90%.[25] The 10-year risk of surgical resection for CD is close to 50%, although this risk has decreased in the past 6 decades.[26] Surgery is not curative, and many patients require repeat surgery.

3. Methods

These data were gathered using a non-systematic focused literature review and a series of search strings consisting of combinations of the search terms “Crohn disease”, “Crohn’s disease”, “risk factors”, “IBD”, “inflammatory bowel disease”, “exclusive enteral nutrition”, “partial enteral nutrition”, “short-chain fatty acids”, “food”, “diet”, “nutrition”, and “microbiome”. We searched the databases “PubMed”, “ResearchGate”, and “Google Scholar”. Papers of relevance were included, with no strict inclusion or exclusion criteria. Studies not in English were

excluded, however. In addition, studies were identified after cross-checking reference lists from the included papers. Due to the similarities between Crohn disease and ulcerative colitis, some studies focusing on UC were considered as well.

4. The role of the gut microbiome in the pathophysiology of Crohn disease

4.1. The healthy human gut microbiome

A metagenomic sequencing of the healthy human gut has determined that it contains bacterial, archaeal, eukaryotic, and viral genes, with 99,1% of the genes being bacterial.[27] Estimated number of different detectable bacterial species in each individual was at least 160, but across the whole cohort approximately 1150 different bacterial species were estimated. The most represented bacteria phyla, which accounted for 90% of those represented, were *Firmicutes, Bacteroidetes, Proteobacteria,* and *Actinobacteria*.

Most gut microbes are either harmless or of benefit to the host. The gut microbiome is involved in extracting nutrients from our diets, protecting against gastrointestinal pathogens, and maturation and normal function of the immune system.[28,29] The human gut is colonised at birth, with the composition changing during the first one to three years of life. During this period, the microbiome is establishing, rendering them particularly susceptible to external factors, like antibiotic use and diet.[30,31]

The gut microbiome has mechanisms to protects its composition and diversity and is therefore relatively resilient to external factors. However, this resistance can be overcome by long-term changes in diet, drugs, prebiotics, or probiotics. In the absence of these factors, the gut microbiome stays relatively constant.[32]

Short-chain fatty acids such as acetate, butyrate, and propionate, are the main products of intestinal bacterial fermentation dietary fibre. SCFAs, especially butyrate, are recognised as having anti-inflammatory effects both in vitro and in vivo.[33–35] SCFAs are sources of energy for the human host, but they also interact with the

immune system by acting as signal transduction molecules via G-protein coupled receptors, as epigenetic regulators of gene expression by inhibition of histone deacetylate, and as inhibitors of NF-κB.[35–37] SCFAs also promote generation of peripheral regulatory T-cells, which promote gut health and homeostasis.[38–40]

4.2. The gut microbiome in Crohn disease patients

E. Sonnenburg and J. Sonnenburg compared the microbiota of Western populations with those of non-Western populations, and found them to be significantly different in the aspect of which bacteria are present and their proportions.[41] They also found the microbiome of Western populations to be less diverse than that of non-Western. These factors could be involved in explaining the polarization in incidence of IBD between Western and non-Western countries.

Dysbiosis, the disruption to the normal balance of the gut microbiota, has been implicated in the pathogenesis of IBD, as well as obesity, malnutrition, neurological disorder, and cancer.[28] The increased risk of CD in dysbiosis is highlighted by the degree to which formula-feeding and antibiotic use in infancy are established risk factors in the development of IBD. A meta-analysis with the aim of examining the association between breastfeeding in infancy and the risk for ICD found that ever being breastfed was associated with a lower risk of CD, with an odds ratio of 0.71.[12] This association was dose-dependent, with the strongest decrease in risk being when the infant was breastfed for at least 12 months (OR 0.20). Antibiotics use in infancy was associated with an odds ratio of developing IBD of at least 2,58.[31] 75% of these cases were CD, the remainder UC.

The aforementioned metagenomic sequencing project sequenced the gut of IBD patients and compared them to the gut of healthy persons. Microbiome composition and diversity varied between healthy individuals, but the bacterial diversity of IBD patients was markedly reduced compared to healthy, with CD patients having even less diversity than UC patients.[27]

In addition to an overall decrease in biodiversity, IBD is also associated with a reduction in specific bacterial taxa, including *Faecalibacterium, Firmicutes, Bacteroidetes, Lactobacillus,* and *Eubacterium*.[42–46] Several studies examining the effect of temporary faecal stream diversion on Crohn disease treated with surgery showed that inflammation and recurrence downstream of the diversion did not occur until after re-anastomosis.[47,48] This suggests that inflammation in CD is dependant on factors in the faeces.

IBD is associated with a decrease in SCFA-producing bacteria, most notable *Faecalibacterium prausnitzii*.[46] *F. prausnitzii* is well established as a marker of a healthy gut[37], and decreased abundance of *F. prausnitzii* was significantly associated with increase in Crohn disease Activity Index, C-reactive protein levels, and erythrocyte sedimentation rate,[49] as well as increased CD recurrence.[37] In one study, the prevalence of Faecalibacterium species was significantly reduced in CD patients, with *F. prausnitzii* being present in 80% of healthy subjects but only 15,8% of CD patients.[46] *F. prausnitzii* exhibits anti-inflammatory effects, partly due to secreted metabolites blocking NF-κB and IL-8 secretion.[37]

IBD is also associated with an increase in Enterobacteriaceae, including E. coli and Enterobacter, as well as Fusobacterium species and Clostridium species compared to healthy subjects.[46,50,51] Certain opportunistic pathogens, including Proteus, Ruminococcus, and Haemophilus species were only found in CD patients, not in healthy subjects.[46] The simultaneous presence of Clostridium species and E. coli and the absence of Faecalibacterium was as much as 100 times more likely to be found in CD patients than in healthy subjects.[46]

Braun et. al. investigated the microbiota of CD patients in remission and compared the microbiota of those who went on to develop a flare-up to those who remained in remission.[52] The microbiota of patients in remission who subsequently flared showed

significantly reduced abundance of Christensenellaceae and Muribaculaceae and significantly increased abundance of Gemallaceae. Notably, higher microbial instability in the remission phase was associated with a significantly higher risk of a subsequent flare (hazard ratio 11.32, 95% confidence interval 3 – 42, p = 0.0035).

Whether the intestinal dysbiosis in CD precedes the pathogenesis of the disease or a is result of the pathogenesis of the disease is unclear. Obtaining biopsy samples in individuals before they develop CD is difficult. One study tried to circumvent this issue by comparing the microbiome of aphthous ulcers in people with CD to the microbiome of their oral mucosa which was unaffected by ulcers, as well as to the microbiome of healthy volunteers. The authors found that the microbiome of the aphthous ulcers did not show the dysbiosis which is characteristic for Crohn disease, and that the microbiome of the ulcers corresponded to that of the unaffected oral mucosa.[53] Because aphthous ulcers usually develop before transmural inflammation and clinical manifestations of Crohn disease, or before a new flare, the authors concluded that their data suggest that intestinal dysbiosis in CD is a consequence of the inflammatory disease process, rather than preceding it.

In paediatric CD, therapy with either anti-TNF drugs or exclusive enteral nutrition (EEN) reduces, but does not eliminate, dysbiosis.[54] In another study[46], mesalazine (*n* = 9), corticoids (*n* = 1), moderate immunosuppressors (*n* = 7), and anti-tumor necrosis factor antibodies (*n* = 1) had no effect on the microbiota composition of the patients, although the small sample sizes make it impossible to draw conclusions.

5. Dietary habits in Crohn disease patients

CD and UC patients often identify foods which they believe ameliorate or exacerbate their IBD symptoms.[55,56] In one study[56], 57% of IBD patients felt that diet could trigger a flare-up. 60% of patients reported worsening symptoms with certain foods. In another study, foods frequently reported to worsen symptoms included vegetables,

spicy foods, fruits, nuts, fried foods, milk, red meat, soda, popcorn, dairy products, alcohol, high-fibre foods, corn, fatty foods, seeds, coffee, and beans.[55] Yoghurt, rice, and bananas were more frequently reported to improve symptoms.

There is a notable heterogeneity of the group of foods reported to worsen symptoms. It includes both foods which are potentially favourable, like vegetables, fruits, nuts, seeds, and high-fibre foods, but it also includes foods which are potentially unfavourable, like fried foods, red meat, soda, alcohol, and fatty foods. One explanation could be that the foods generally assumed to be healthy do not exacerbate the disease process but simply cause symptoms as they would in individuals without IBD. Another explanation could be that there is such a large inter-individual variability in the response of Crohn disease to certain foods that it's difficult to draw conclusions regarding similarities and differences in which foods worsen symptoms.

The aforementioned study[55] which examined which foods IBD patients report to worsen or improve their symptoms also found that these patients usually avoid foods which they believe worsen their symptoms. Among the foods which IBD patients usually avoid were many nutrient-rich foods, especially vegetables, fruits, nuts, seeds, and beans. IBD patients may be at risk for nutritional deficiencies if they replace nutrient-rich foods with nutrient-poor foods in an attempt to ameliorate their symptoms.

This tendency was highlighted by a recent case-control study[57] which compared the habitual dietary intake of IBD patients with that of population controls. It compared the dietary intake of macronutrients and 25 food groups of 493 IBD patients and 1291 controls via a food frequency questionnaire. Compared to the population control, CD patients consumed more non-alcoholic drinks, potatoes, savoury snacks, sugar, and sweets, but less alcohol, dairy, nuts, pasta, and prepared meals.

The European Society for Clinical Nutrition and Metabolism (ESPEN) recommend adult IBD patients with active disease a daily protein intake of 1,2 – 1,5 g/kg body weight, and patients in remission a daily intake of 0,8 g/kg body weight.[58] The aforementioned case-control study[57] found that 86,7% of IBD patients in the study with active disease had a daily protein intake below the recommended 1,2 g/kg body weight, and 38,6% of patients in remission had a daily protein intake below the recommended 0,8 g/kg body weight.

6. Specific dietary interventions

6.1. Dietary fibre

The potential of short-chain fatty acids in the treatment of IBD has been theorised.[34,35] Administration of a trans-galacto-oligosaccharides, a form of oligosaccharides, stimulated the growth of bifidobacteria and changes the intracolonic fermentation metabolism to produce more SCFAs.[59] The role of decreased fibre intake in the increased incidence of disease has been known for decades.

Several cell culture and animal model studies have shown that butyrate can strengthen epithelial barrier function and decrease intestinal permeability.[60–62] However, a ex vivo study from 2020 on the acute effects of butyrate on colonic hyperpermeability of human colonic specimens found that butyrate had no protective effects against development of colonic hyperpermeability induced by a mast cell degranulator.[63]

A 2017 study found that β-glucan significantly attenuated mast cell degranulator-induced paracellular hyperpermeability in both CD patients and controls.[64] Żyła et al. found that dietary oat β-glucan significantly decreased inflammatory markers, decreased lymphocyte infiltration and increased feed intake in a Crohn disease rat model[65], but Heinsbroek et al. found that orally delivered β-glucans aggravate intestinal inflammation in a mouse model.[66]

In 2020, the Nutrition Cluster of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) collected the best available evidence to date and created a dietary guidance consensus document.[67] They concluded that available evidence in humans was too lacking to reach strong evidence levels for recommendations for or against certain dietary components, which highlights a need for further human studies in this field. Regardless, they found low levels of evidence to recommend increased exposure to fruits and vegetables in CD patients, and to recommend restriction of intake of saturated and trans fats. A notable exception to the increased fruit and vegetable intake were for those CD patients with fibrostricturing disease, who they recommended should restrict insoluble fibre intake, although with a very low level of evidence. Because of the lack of human studies, some conclusion had to be drawn from animal studies.

A randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides (FOS) as food supplements in patients with active CD from 2011 found no significant differences in CDAI between the FOS groups and the placebo group[68]. The group receiving FOS supplement had reduced proportions of IL-6-positive lamina propria dendritic cells and increased dendritic cell staining of IL-10, but there were no differences in faecal concentration of bifidobacteria or F. Prausnitzii between the groups before or after the intervention. These interventions lasted only for 4 weeks. The FOS supplement group experienced significantly increased incidence and severity of gastrointestinal symptoms.

A 1979 trial by Heaton et al. involved 32 CD patients who were prescribed an unrefined-carbohydrate diet and followed for a mean of four years and four months[69]. The clinical courses of these 32 patients in the intervention group were then retrospectively compared with 32 matched patients who had received no dietary instruction. The study found that the interventional group had a significantly lower number of hospital admissions, as well as shorter hospital stays.

The authors of the trial constructed a booklet which advised the trial participants on the dietary changes they were to follow. The booklet included advice on reducing refined sugar, replacing white flour and white rice with wholemeal flour and unpolished rice, encouraging consumption of fruit and vegetables, etc.

On the other hand, a 1987 randomised controlled trial by Ritchie et al. involved 352 patients with inactive or mildly active CD who were randomly allocated into one of two groups, one group taking a diet unrestricted in sugar and low in fibre, and the other group taking a diet with little or no sugar and high in fibre[70]. The dietary changes were the same as those advocated in the 1979 study. The trial lasted for two years. The RCT found no significant differences in any of the end points, including need of surgery, hospital admission, withdrawing from the trial due to more symptoms, or requirement of outpatient treatment.

These seemingly contradictory findings may be at least partially explained by certain factors, in this author's opinion. First, the 1979 trial, which found the dietary changes to be beneficial, lasted longer than the trials which didn't show any benefit. It is possible that beneficial effects of dietary changes in CD are not apparent until after more than two years of these changes, and the 1979 trial did not disclose a timeline for the intervention, which could underline this point. The 2011 RCT lasted only 4 weeks. Second, the 1987 trial recruited only CD patients with inactive or mildly active disease, whereas the 1979 trial did not discriminate on disease activity. It is possible that beneficial effects of dietary changes appear only, or perhaps earlier, in more severe CD than in less severe disease. Third, although the dietary changes advocated were the same in the 1979 and 1987 trials, they might've been interpreted differently by the clinicians and dietitians explaining them to the trial participants. Fourth, it is possible and perhaps even likely that modification of only one or two macronutrients (namely, carbohydrate composition and fibre intake) is not in and of itself enough to induce significant changes in Crohn disease pathophysiology, and that the other

components of the diet also play a role. If the theoretical anti-inflammatory effects of fibre are counteracted by pro-inflammatory effects of other parts of the diet, the beneficial effects may be reduced or completely counteracted. It is possible that that the restriction of refined carbohydrates caused other "secondary" changes in the trial participants' diets, such as increased intake of red meats, alcohol, or artificial sweeteners, foods which are theorised to have a negative impact on gut health. Fifth, it is possible that dietary factors are more important in maintaining disease remission and in preventing CD in those at high risk and less important in reducing severity of acute illness. The authors of the 2011 study reached the same conclusion.

6.2. Exclusive enteral nutrition and partial enteral nutrition

Exclusive enteral nutrition (EEN) is the most extensively researched dietary intervention to induce remission in mild to moderate CD both in children and adults, but it is more widely used in paediatric populations compared to adults[71]. EEN involves giving patients exclusively liquid formula as their only source of energy for a set amount of time, often at least six weeks. This liquid formula must be nutritionally complete. In a number of case series and clinical trials, EEN has been shown to induce clinical remission in approximately 70-80% of paediatric patients.[72,73] The 2014 consensus guidelines of ECCO/ESPGHAN on the medical management of paediatric Crohn disease has EEN as the first-line therapy to induce remission in children with active mild-to-moderate luminal CD.[74]

EEN is difficult to adhere to, particularly in adults, and as such is not as widely studied in adults as in children. This is likely due to disruption of normal adult life, poor palatability, lack of experience, and lack of guidance, but not due to inherent differences in the efficacy of EEN in adults.[75] Indeed, a 2013 review article found that the main barrier to successful treatment with EEN in adults was adherence, with up to 41% of patient dropping out of EEN treatment.[76] The article also found no significant difference between EEN and corticosteroids in inducing remission. Due to

lack of evidence and low compliance, consensus clinical guidelines in Europe and North America do not recommend EEN as first-line therapy to induce remission in adults.[77,78]

Partial enteral nutrition (PEN), the practice of giving a certain portion of the patient's energy needs by liquid formula and the remainder by normal foods, has not shown efficacy in inducing remission neither in paediatric nor in adult CD patients. The discrepancy between the efficacy of EEN and PEN suggests that the effect of the former depends, at least in part, on exclusion of free diet. Likely, there are some foods in the "default" diet of CD patients which are included or excluded and which influence the activity of the disease.

6.3. Crohn disease exclusion diet

The findings of a 2014 clinical trial, which examined the efficacy of the combination of PEN and a Crohn disease exclusion diet (CDED), support this hypothesis. It found that the combination of PEN and the exclusion diet (CDED) for 6 weeks was efficacious in the induction of remission in children and young adults.[79] Half of the estimated daily calorie requirement was provided by PEN, and half from the diet. The primary endpoint was remission (defined as Harvey-Bradshaw Index (HBI) < 5 in adults or < 3 in children), and the secondary endpoints included normalisation of CRP, a drop in HBI of at least 2 points (defined as a *response*) or change in specific blood tests from baseline such as haemoglobin, albumin, ESR, and CRP.

After 6 weeks, remission was reached in 33/47 (70%) of children and 9/13 (69%) of adults. Among children, remission was achieved more frequently in those with mild and moderate disease (75% and 71%, respectively), compared to those with severe disease (33%). Virtually no study participants experienced an increase in CRP. The components of the Crohn disease exclusion diet used is shown in figure 1.

Allowed Foods Daily Meals: Foods may be grilled, fried, baked, boiled, and broiled
Fresh Chicken Breast, Fresh Fish—unlimited
Fresh Unprocessed Beef Steak (lean meat such as sirloin)—once a week
White Rice
Rice Noodles
2 fresh Potatoes (Peeled), frozen potatoes not allowed, not to be consumed at same meal
2 Eggs
2 Tomatoes
2 Cucumbers (peeled)
1 Carrot (shavings)
Fresh Spinach (side portion)
1 Apple (peeled—if no tight stricture)
2 Bananas
1 Avocado
Few Strawberries
Slice Melon
Allowed Condiments for cooking:
Olive oil, Canola oil
Salt, Pepper, Paprika, Cinnamon stick
Fresh Herbs (Mint leaves, oregano, coriander, rosemary, sage, basil, thyme)
Fresh onion or garlic or ginger
Fresh Carrot shavings for salad, rice or soup
True Honey
Table Sugar (2–3 Teaspoons a day for Cooking or Tea)
Beverages
Water, Soda, herbal teas
One glass of freshly squeezed orange juice daily (not from cartons or bottles)
Not allowed
Dairy products of any kind, margarine
Wheat, breakfast cereals, breads and baked goods of any kind, yeast for baking
Gluten-free products not listed above, Soya products, potato or corn flour
Processed or smoked meats and fish (sausages, luncheon meats, salamis, fish sticks)
Sauces, salad dressings, syrups and jams of any kind
Canned products and Dried Fruits
Packaged snacks (potato chips, pretzels, popcorn, nuts, etc)
All soft drinks, fruit juices and sweetened beverages, alcoholic beverages, coffee
Candies, chocolates, cakes, cookies and gum

Figure 1. This figure shows the components, inclusions, and exclusions of the Crohn disease exclusion diet (CDED) which was used in the 2014 study by Sigall-Boneh et al.[79]

After the first 6 weeks of PEN and CDED, those participants who experienced remission were put on a step-down diet for another 6 weeks to ease the transition to their habitual diet. This step-down diet involved a 25%/75% split of calories from PEN and diet, respectively, while also allowing small amounts of bread, nuts, fruits, legumes, and vegetables. At week 12, 27/32 (84%) of these participants were still in

remission. Three of those who relapsed between week 6 and 12 repeated the CDED again, and 2/3 regained remission.

The CDED is strict, excluding several foods which may be part of a normal diet. Despite this, of the 47 participants in the original study, only 5 (11%) were not compliant. However, the age of the participants was that of children and young adults (age range at onset 6 – 28), and it is known from studies on EEN in adults that children and young adults may tolerate these drastic dietary changes better than other adults. Further studies are needed to examine whether this disease is tolerable in the larger population.

In the study, seven patients used the CDED without PEN (due to refusal of formula). Of these seven, six entered remission. No conclusions can be derived from a sample size this small, but further studies should examine the efficacy of CDED alone. However, the nutrient composition of the Crohn disease exclusion diet alone may not be optimal, potentially lacking certain vitamins and micronutrients. As noted in the original study, with the complete exclusion of grain and dairy products, calcium intake may not reach the recommended daily intake.

6.4. CD-TREAT diet

A 2019 study examined the effects of an individualised diet called CD-TREAT and evaluated its effects on healthy adults, children with active CD, as well as animal models.[80] This diet aims to have a similar composition to EEN while being more tolerable than that. To recreate the features of EEN as closely as possible, the CD-TREAT diet matches the macronutrient, vitamin, mineral, and fibre composition of EEN, and excludes certain dietary components, although the original paper only specifies three of them (gluten, lactose, and alcohol). To increase tolerability, the diet considers food preferences. A multivitamin was administered to ensure sufficient intake of micronutrients and vitamins. Figure 2 shows a day's menu of one of the participants.

Breakfast:
1 multivitamin tablet
Full fat milk (360ml)
Rice breakfast cereals (45g)
Apple juice (360ml)
Morning snack:
Pineapple juice (360ml)
1 peeled apple
Lunch:
1 sandwich with white bread (2 slices), cheddar (45g) and cream cheese (45g), lettuce (20g) and peeled cucumber (20g)
1 bowl chicken and rice soup
Afternoon snack:
1 rice pudding
Dinner:
1 portion grilled salmon (180g) with mashed potatoes (260g) and cheese sauce
All dairy products were lactose free; all cereal-based products were gluten free

Figure 2. This figure shows one day's menu of the CD-TREAT diet of one of the participants. The participant was a 15-year-old boy weighing 48 kg and 170 cm. The participant had histopathologically confirmed Crohn disease.

The CD-TREAT diet is more permissive than the Crohn disease exclusion diet (CDED). In contrast to the CDED, the CD-TREAT diet allows multiple food products, most notably lactose-free dietary products, certain cereals, and fruit juices from multiple types of fruit.

The CD-TREAT study had three parts. The first part involved an RCT in healthy volunteers, where the participants were randomised into receiving either CD-TREAT diet or EEN for one week, followed by two weeks of habitual diet, followed by the opposite intervention (participants initially on EEN were prescribed CD-TREAT diet and vice versa). Before, during, and after these dietary changes, stool samples were taken and examined. Multi-omics methodology was employed to interrogate changes in microbiome and metabolic signatures before and after the dietary interventions.

The healthy volunteers found CD-TREAT to be easier to follow and more satiating than EEN. Gastrointestinal symptoms were uncommon for both diets, but abdominal pain and diarrhoea were more common for EEN than for CD-TREAT. The microbiome composition, faecal pH, SCFA, total sulphide, faecal bacterial load, and faecal metabolome significantly changed in the same direction for the 2 diets with many

parallel changes in specific metabolites and species. We can therefore suspect that the two dietary interventions produce similar changes in the GI tract. However, some effects seen in the present study have been previously associated with gut dysbiosis or an “unhealthy” microbiome, but paradoxically associated with decreased disease activity and amelioration of colonic inflammation in children with active CD on EEN. This is a paradox which raises questions regarding our understanding of what a “healthy” microbiome is, as well as questions regarding the mechanism of action of EEN and the pathophysiology of CD.

The second part involved an open-label trial of 8 weeks CD-TREAT with five participants (children with mild to moderate active luminal Crohn disease). One of the participants discontinued CD-TREAT after 9 days because of symptom exacerbation. At the end of 8 weeks of treatment, 4/5 participants responded clinically while 3/5 participants reached clinical remission. Baseline faecal calprotectin decreased significantly by 55% after 8 weeks. Interestingly, a reduction was seen in faecal calprotectin in the participant who discontinued CD-TREAT as well (from 2026 mg/kg at baseline to 1072 mg/kg at 9 days).

The third part of the study involved animal experiments comparing EEN, CD-TREAT, and control groups in rat models of gastrointestinal inflammation strongly associated with microbial dysbiosis. Attenuation of ileitis histopathology scores and decreased expression of pro-inflammatory cytokines interleukin 6 (IL-6) and chemokine [C-X-C motif] ligand 1 (CXCL-1) in the CD-TREAT-treated animals indicate that CD-TREAT can deliver therapeutic benefit in a disease state strongly associated with microbial dysbiosis, a description which fits Crohn disease in humans.

Overall, this randomised controlled trial study found the CD-TREAT diet to be more tolerable and yielding fewer gastrointestinal side effects than EEN, while also inducing a significant clinical response in children with active CD as well as changes in healthy adults and rat models which indicate a therapeutic possibility. At the time

of writing, further clinical trials aiming to study this diet are underway (ClinicalTrials.gov Identifier: NCT04225689).

7. Discussion

Multiple factors point to the diet playing a major role in Crohn disease. As an example, temporary faecal diversion improves gastrointestinal inflammation in Crohn disease, and inflammation and recurrence downstream of the diversion recurs only after re-anastomosis, and not before. Currently, the only dietary intervention which is widely used in the management of Crohn disease and has documentation regarding its efficacy is exclusive enteral nutrition (EEN). EEN is effective in inducing remission in childhood CD. However, it is difficult to adhere to, removing it as a treatment option for most adults. It's also unsuitable for long-term treatment to maintain remission. However, the efficacy of EEN indicates that there should exist dietary interventions which may be useful in the management of CD, and which are based on regular foods rather than food formula, making them more palatable. Such dietary interventions hold more promise for long-term treatment, which may help in maintaining remission.

It is thought that dysbiosis contributes to the inflammatory activity of CD, either directly or indirectly, but studies have shown that currently established pharmacological treatments may not eliminate dysbiosis. Theoretical evidence, animal experiments, and rudimentary human experiments suggest that modulation of inflammatory activity in Crohn disease with dietary interventions (like EEN) may occur partially or wholly through inducing alterations of the gastrointestinal microbiome. Indeed, multiple studies have shown that changes in the microbiome follow changes in diet. However, it is difficult to quantify changes in the microbiome, due to the vast variety in bacterial florae and the significant interindividual variation. It has also proven difficult to predict which changes to the microbiome are beneficial and which aren't, as results sometimes contradict each other.

The mechanism of action of EEN is not well known. It is not known whether the mechanism involves exclusion of certain dietary components, increased intake of certain dietary components, some other mechanism, or a combination of these. It has been theorised that exclusion of certain dietary factors may affect intestinal permeability, enhance translocation or adherence of bacteria to epithelium, or promote a proinflammatory microbiome.

As presented in this paper, exclusive enteral nutrition is efficacious in inducing remission and clinical response, as is partial enteral nutrition combined with a Crohn disease exclusion diet (CDED), whereas partial enteral nutrition alone is not efficacious. The CD-TREAT diet, which excludes certain food components like lactose, gluten, and alcohol, also shows promise. Increased dietary fibre intake does not appear to be helpful. These findings suggest that there are some dietary triggers which may influence gastrointestinal inflammation, and that elimination of some foods or food components is likely an important factor in the mechanism of action of dietary interventions in CD.

Up until now, research has focused on applying the same or very similar dietary interventions to all participants. However, dietary triggers may also be related to personal factors, such as genetics or other environmental factors. As such, dietary triggers may be different on a subpopulation or even an individual level, possibly making identifying universal dietary triggers for all CD patients impossible. If dietary triggers are individual rather than universal, we might see more of a systematic “try-and-see” approach to diet in Crohn disease patients in the future, where the patients exclude suspected high-risk food components one at a time from their diet and monitor the response. However, this is time-consuming, and monitoring treatment response is difficult in such cases.

It is possible that, rather than using dietary interventions alone, combining pharmacological therapy with dietary interventions which ameliorates or eliminates

dysbiosis could improve the efficaciousness of therapy in an additive or synergistic manner, reduce the number of medications necessary and therefore the side effect burden, and/or reduce the frequency and/or intensity of remissions.

While it is known that dysbiosis is associated with CD, it's not well known whether it is a contributing cause to the disease or its recurrence, or whether it's a result of the disease, or both. Longitudinal studies aimed at assessing the gut microbiome before disease onset and throughout the disease development would provide further insight into the question as to whether dysbiosis precedes the development of Crohn disease or whether it succeeds it. This would be important in the future research into therapeutic options.

8. Conclusion

Crohn disease (CD) is a chronic inflammatory bowel disease which causes significant patient morbidity and healthcare costs. Most currently available therapies for Crohn disease are anti-inflammatory medications. Although often efficacious, these medications are not without risks and side effects, some are very expensive, and not all patients respond to them. The disease is chronic and the treatment often lifelong. As such, the scientific community has been seeking safer, cheaper, and more effective treatment options for Crohn disease and ulcerative colitis.

There is theoretical and practical evidence which points to the possibility of certain diets or dietary modifications to be highly efficacious in the induction and maintenance of remission in Crohn disease. Exclusive enteral nutrition (EEN) is already known to be efficacious but has limited use due to poor adherence to treatment, especially in adults, and especially in the long term. This paper has presented novel dietary interventions which show promise, namely the CD-TREAT diet and the combination of partial enteral nutrition (PEN) and a Crohn disease Exclusion Diet (CDED). However, more research is necessary to determine whether any of these interventions should be recommended for wide use. Future research needs to determine whether the positive effects of these dietary interventions seen in smaller trials are also present in larger, higher-powered trials. Research also needs to determine which interventions are the most efficacious, how dietary interventions interact with pharmacological therapy, whether certain subpopulations of CD patients benefit more from certain interventions, and whether dietary interventions are universal or must be individualised or adapted to certain sub-populations.

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