Enteral Nutrition in IBD Patients

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Inflammatory bowel disease (IBD) is a chronic disease mediated by the immune system and is characterized by inflammation of the gastrointestinal tract. One of the possible treatments for this pathology is a change in the type of diet, of which enteral nutrition (EN) is one.

inflammatory bowel diseases | enteral nutrition | systematic review | meta-analysis | Crohn's disease

1. Introduction

Inflammatory bowel disease (IBD) is a chronic disease mediated by the immune system and characterized by the inflammation of the gastrointestinal tract. IBD includes Crohn's disease (CD) as well as ulcerative colitis (UC) [1]. UC affects the large intestine and is generally observed as a superficial ulcer due to an inflammatory reaction localized to the mucosa and the submucosa. However, CD occurs all along the intestinal tract (from mouth to anus) and involves the entire intestinal layer [2].

The prevalence and incidence of IBD has increased worldwide and is increasingly diagnosed in young individuals [3]. As it is a chronic, incurable, and low-mortality disease, it is expected that the decrease of the global burden of the disease in the next decade will require a two-pronged solution that implies research on prevention interventions as well as innovations in the care of these patients [3][4].

The etiology of IBD is still greatly unknown, and recent evidence indicates that the genetic susceptibility of the individual, the environment, the intestinal microbial flora, and the immune responses are all factors that are involved and functionally integrated in the pathogenesis of IBD [5]. IBD can provoke various symptoms that include abdominal pain, low fever, fatigue, weight loss, diarrhea, bloody feces, etc. [6].

Within the identification of the environmental risk factors, diet is one of the most important as it regulates intestinal inflammation by modifying the intestinal microbiota, which has an effect on the gastrointestinal permeability [7][8]. Therefore, it can induce the expression of disease genes and determine the cell's phenotype and function in IBD [7][8]. One of the possible treatments for this pathology is a change in the type of diet [9].

One of the potential changes in diet is the use of enteral nutrition (EN), which is based on the administration of enteral foods/formulas through different means. These foods are nutritionally-complete liquid mixtures of pre-digested foods that have carbohydrates such as simple sugars, fats such as different types of oils, and nitrogen as

protein, along with vitamins and minerals [10]. Within the elemental formulas, different classes can be distinguished as a function of the nitrogen source: elemental formulas are based on amino acids, semi-elemental formulas are based on oligo-peptides, and polymeric formulas are based on whole proteins [11].

Diverse authors have highlighted that EN, especially in the form of exclusive enteral nutrition (EEN), is a type of therapy established to induce the remission of CD in the infant population, although its role as a first line therapy for CD in adults has not been defined yet and its mechanism of action for palliating the symptoms of IBD is not completely understood [9][12]. Authors such as Guagnozzi et al. suggest that the interaction between the composition of specific dietary formulas or nutrients and IBD should be investigated to add new knowledge to the etiopathogenesis of the disease in nutritional intervention [13].

2. Current Insights on Enteral Nutrition in IBD Patients

Our results included 30 studies (1070 participants). All trials included had a broad scope and had a very varied methodological and clinical heterogeneity. The variables collected were very diverse, with CDAI, CRP, and ESR being the most common. The sample sizes of the studies included were generally small ($n < 30$), thus, a meta-analysis was needed in order to arrive at better conclusions.

A cure for IBD is not known, however, there is evidence of remission and improvement of the symptoms with EEN, which implies the exclusive consumption of an elemental or polymeric substance for many weeks [14], as shown by many of our results. Despite the lack of correlation between IBDQ and the CDAI, correlations were observed between both indexes starting at week 4 of the treatment. A study that focused on the gall bladder was even found, which showed its improvement after day 36 of treatment administration; therefore, aside from reducing the activity or inducing the remission of the disease, this diet could have beneficial effects on organs related with the digestive system [15][16].

The EN formulas tended to contain macronutrients such as amino acids or simple carbohydrates, along with micronutrients such as vitamins. The proteins, carbohydrates, and fats do not reach the ilium or the colon as they are absorbed in the duodenum and jejunum. As for the amino acids they contain, they were named as elemental formulas if they contained free amino acids, semi-elemental if they contained peptides, and polymeric if they contained whole proteins [17]. Different formulations exist, but the ones that do seem to have a positive effect on the maintenance and remission of the disease are elemental and polymeric diets [10][18]. The efficacy of an EN diet does not depend much on it being elemental or polymeric, as shown by some of our results [19][20], since, a priori, both have the same potential for inducing a remission [21][22][23]. However, the meta-regression conducted indicated that a polymeric diet could decrease the CRP better than an elemental one. Additionally, a distinction could be made between them when looking at the economic burden entailed by the use of one or the other and the acceptability by the patients, meaning that, in the adherence to the dietary treatment, the polymeric ones tend to be more accepted by the patients, as they are better tasting [24][25]. The elemental foods are less tolerated with mouth feeding, and generally require a nasogastric tube, which entails complications and patient discomfort. In contrast, the polymeric EN is more tolerable through the mouth by patients, making it the first option for the ill [26][27].

As for the formulation of the EN, studies have also been conducted on the benefits or not of an EN diet rich in fats as opposed to an elemental EN. Just as in other studies, the results of the clinical trials are controversial. Some studies have demonstrated the beneficial effect of the enteral formula rich in fats [28], while others did not show any effect [29] or less beneficial effects [30]. Despite what has been said, some studies have suggested that an EN high in fats could improve gastrointestinal motility and improve the ilium after an operation [31], reducing damage to the intestinal mucosa barrier and the underlying mechanism that could be associated with its antioxidant action after surgical intervention [32].

EEN, combined with some types of medication such as antibiotics [33], seem to improve the disease's symptoms. Just as shown by our results, EN combined with other types of pharmaceuticals such as prednisone, corticosteroids, and sulfasalazines show a significantly continuous high rate of remission [34][35]. On the other hand, the combination of EN with steroids does not seem to have significant differences in the probability of a relapse [36], perhaps because the steroids do not address the damage produced in the intestinal mucosa, which is the greatest predictor of complications over time [37][38].

Although the mechanism that nurtures the healing of the mucosa by the EN has not been completely determined as of yet, it has been shown that a polymeric formula was as effective as the Infliximab inhibitor of tumor necrosis factor (TNF)-α, and is higher than the hydrocortisone in the maintenance of the function of the intestinal barrier [39]. This is perhaps the reason why significant differences were not found in a study conducted by Gasull et al. in 2001 that utilized two polymeric EN formulas, with the response being similar in both [40]. Additionally, in another study conducted with two polymeric formulas for five weeks, a significant relationship was not found between the treatment with different EN and the changes produced at the level of the disease's activity [41].

As for the use of elemental and semi-elemental EN, the results were very similar. For example, Mansuf et al. achieved the clinical remission of 16 patients in four weeks with both formulas, and the reduction of the CRP was significant in both groups [42]. The mechanism of action of the semi-elemental diet could be multifunctional, just like as the elemental one, decreasing the intestinal permeability and thus decreasing the loss of fluid. The semi-elemental diet could also reduce the commensal intestinal bacteria that play a role in intestinal inflammation [43][44]. Thus, the use of these types of diets is advisable, either with the use of an elemental or semi-elemental formula for the management of different gastro-intestinal disorders [45].

In 2013, Yun Feng et al. [46] found significant differences between groups subjected to EEN and EN plus an oral diet, although it is interesting to note how the patients refer to a greater subjective well-being when they take EN together with the oral diet when compared to those who are not treated with supplemented EN, despite the biochemical parameters being very similar [47][48]. Some studies suggest that a partial enteral nutrition supplemented with different diets such as elimination, anti-inflammatory, auto-immune diets, or diets low in FODMAP (Fermentable Oligo-, Di-, Mono-saccharides and Polyols) could be beneficial for UC and CD [16][21], although larger controlled assays are needed to back their use [49]. Even patients who were subjected to EN before their operation experienced benefits, not only in their nutritional state, but also with a reduction of inflammation in their disease [50], with patients also experiencing improvements after said intervention [51].

Historically, EN was used and is used as a complementary nutritional treatment for patients with complicated IBD that leads to worrying malnutrition, thus improving their nutritional state [25]. However, the meta-regression from our study showed an inverse relationship between the period of treatment with EN and the improvement shown through the CDAI, that foreseeably, the patients who are subjected to prolonged EN could stop noticing its benefits.

The EN was utilized as an induction therapy for active IBD [25], but it is important to know which EN formulas can be used to boost their anti-inflammatory effects, as there is evidence that supplementary EN is not sufficient for inducing remission, so that it would have to be used exclusively to be able to obtain its anti-inflammatory effect [52] [53]. At present, it is well-established that EEN has a strong anti-inflammatory effect with a reduction in the systemic and mucosa inflammatory parameters in a few days, however, the EEN as a long-term therapy is still a challenge, given its lack of palatability and the lack of data to analyze the efficiency of EEN as a maintenance diet [54].

Diverse studies have shown that clinical remission and healing of the mucosa is possible through different nutritional regimes [55]. As for the debate about which is healthier, EN or PN, our results showed that there are studies in which the effectiveness of both seems to be significantly the same for the improvement of the CDAI [56] [57]. Bearing in mind that the dietary antigens could be important stimulants for the immune system of the mucosa, intestinal rest with total parenteral nutrition (TPN) is considered as the main option for achieving this rest and for correcting possible nutritional deficits [58]; however when compared to the EN, it does not seem to provide greater benefits. In fact, in one of the studies included in our review [59], EN was the one that seemed to provide the greatest benefits to the patients and to reduce the costs, personal as well as economic, of the different dietary treatments [60].

According to European guidelines, the acceptability and the obligatory compliance of the EN are the greatest obstacles found by different researchers when dealing with EN studies. There are clear differences between the studies shown in terms of healing of the mucosa, and therefore the remission of the activity of the disease, which makes them difficult to compare. What is known, however, is that the EEN is a real alternative to immunosuppressive therapy, which exerts its main therapeutic effect on the microbiota, thus reducing intestinal permeability, enhancing barrier defense, and promoting a reduction of pro-inflammatory cytokines [61][62].

This study is not exempt of limitations. With respect to the systematic review, seven articles were not recovered, so our results could be altered. However, the small variability observed through the meta-analysis implies that these articles could substantially vary the results obtained, and in fact, the sensitivity study that analyzed the publication bias showed little alterations on the effect size as well as its confidence interval. Although the quality of these studies has not been introduced in the meta-regression, all the articles that were utilized with this technique were considered to have sufficient quality, so we do not believe that the quality could introduce bias in the findings.

3. Conclusions

EN has been shown to have efficacy for the treatment of CD and is compatible with other medicines. As for the CDAI or the rates of remission, there were no differences between EN and PN. Polymeric formulas, when

compared to elemental ones, have shown better results with respect to the CRP. The long-term treatment could dilute the good CDAI results that are obtained at the start of EN treatment.

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