Role of Nutrition in Inflammatory Bowel Disease (IBD): New Therapeutic Approaches and Recent Outcomes

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Abstract: Inflammatory bowel disease (IBD) is the generic term given to a heterogeneous group of disorders of the gastrointestinal tract that are characterized by chronic inflammation. The major forms of IBD are Crohn’s disease (CD) and ulcerative colitis (UC), which are increasing in incidence, prevalence and severity in many countries; these are characterized by intestinal inflammation and are believed to involve complex interactions between genetic, immunological and environmental factors. The incidence continues to rise, both in low and in high-incidence areas. Several dietary regimes may modify disease symptoms, in part through their actions on the host microbe. However, other dietary factors could affect the microbiotic or genetic expression in IBD patients in different ways. The purpose of this review is to discuss the most recent evidence from the literature on the use of nutritional therapy in the treatment of IBD and to review the role of environmental factors on the progressive increase of prevalence. The epidemiological data reveal an increasing incidence of IBD in recent years, which may be the result of increased intake of simple sugars and consumption disproportionate of fat (saturated and unsaturated). Intestinal permeability and inflammation could improve with proper diet in protein, probiotics and FA (n-3 and n-6). Diet and the host microbiota are likely to play important but as yet poorly defined roles therefore, is necessary to continue investigating to implement molecular findings in clinical treatments or adjunctive therapies.

Keywords: Inflammatory Bowel Disease, Nutrients, Fatty Acids and Treatment.

INTRODUCTION

Inflammatory bowel disease (IBD) is the generic term given to a heterogeneous group of disorders of the gastrointestinal tract that are characterized by chronic, relapsing intestinal inflammation. The major forms of IBD are Crohn’s disease (CD) and ulcerative colitis (UC), are distinguished by their location and severity. CD is more severe, common clinical features of this include abdominal pain, diarrhea, weight loss, and fever, can affect any part of the gastrointestinal tract, is typically discontinuous, and involves all layers of the intestinal wall. In contrast, UC is continuous, restricted to the colon and the rectum, and affects only the mucosal layer of the intestinal. Clinically, both conditions usually begin gradually, but they can start abruptly and sometimes even present as fulminant disease. The incidence varies according to geographical location and differential diagnosis into CD and UC is made on the basis of clinical, radiological, endoscopic, and histological features [1, 2].

At present the pathogenesis of IBD is largely unknown nevertheless, studies described that a combination of environmental triggers and aberrant immune response to commensal microbiotic in a generically susceptible host underlines the CD and UC [1, 3]. Genetic wide association studies have largely characterized more than 100 loci housing genetic alterations associated with the risk of suffering from IBD [4]. However, we are still far from understanding the functional significance of these alterations and their pathophysiological implications in IBD.

Treatments in IBD are costly, often insufficient, and can be accompanied by severe side-effects. Some patients may have extraintestinal manifestations (e.g., osteoporosis, weight loss, anorexia) secondary to treatment; hence, there is an urgent need for new therapeutic targets or adjunctive therapies more efficient for IBD patients [5]. On the other hand, nutritional therapy is important because the intestinal inflammation suppresses appetite and increases catabolism. In CD and UC inflammation causes abdominal pain and diarrhea resulting in patients avoiding eating, in order to limit these symptoms besides lose protein from their ulcerations, in this sense, dietary intervention to replace deficiency is essential; also have been described some forms to improve quality of life, malnutrition and underweight in these patients, through nutritional therapies with supplementation, parenteral nutrition and immunonutrition [6].
IMPACT OF EATING BEHAVIORS ON PREVALENCE OF IBD

The incidence and prevalence of IBD are increasing worldwide, with moderate to high incidence rates in countries from Western and Northern Europe or North America. In Eastern Europe the increase of patients with IBD in the last two decades is likely due to the gradual change in the alimentation, became more westernized; the diet traditionally used to have large amounts of fruit and fish and now the diet includes processed meat, refined grains, high-fat food, sweets and high sugar drink [7, 8].

The concept that IBD is a multifactorial and polygenic diseases has been described over time. However, Lovasz et al. explained that the difference in the genetic and immunological background is unlikely to contribute to the rapid changes in the epidemiology of the disease in Eastern Europe; since the frequency of risk genetic and serologic markers is similar to that observed in Caucasian populations in the developed, these observations confirm the implication of the micro and macro nutrient in the new form of to eat the foods [9].

In a study in the United States of America (USA) the authors described that during the period 2004 to 2009 the prevalence of IBD increased to nearly 1.2 million patients with IBD (>20 years) and 5% of all cases are of pediatric age (<20 years) [10]. The findings in USA could be related with published by Song et al. which describes that intakes of carbohydrates (CHO) have increased in the last years. In this country the total and added sugars have been reported as the major source for energy intake in children and adolescents, the consumption of sugar-sweetened drinks was associated with childhood obesity and another diseases like IBD [11].

Jakobsen et al. in a study described risk factors for IBD identified in children, such as high sugar intake (IBD: OR:2.5(1.0-6.2); CD: OR:2.9(1.0-8.5)); and in contrast protective factors were daily versus less than whole meal bread consumption (IBD: OR:0.5(0.3-0.9); CD: OR:0.4(0.2-0.9)) [12]. The results in this study help us to understand about of environmental factors that could be more commonly involved in the increasing prevalence of IBD over time.

METABOLIC CHANGES DURING IBD AND NUTRITIONAL TREATMENT

Inflammation has been associated with down-regulation of metabolism, digestion, absorption and excretion of nutrients, and up-regulation of cellular stress and immune responses [13].

Recent evidence from genetic and immunologic studies in IBD suggests that metabolism and inflammation are tightly linked processes that cross-regulate each other. In this sense, is important the recognition of limitations in the correct absorption of essentials macro and micro nutrients due to the inflammation present in the cells of the intestinal tract and metabolic changes in these patients [13, 14].

CHO and Proteins

The balance between protective and commensal luminal bacterial species is lost probably for the metabolic changes causing increased mucosal permeability and insufficient mucosal clearance, the maintenance of microbiotic and host is supported by the balance of microbiotic and immune activation that may be disturbed in IBD. Other hand, the activation of Toll-like receptor (TLR) 4 by bacterial lipopolysaccharide (LPS) contributes to disease progression. In connection with LPS-activated TLR4, the alkaline phosphatase (iAP) enzyme has received increasing attention as a factor responsible for mucosal defense.

iAP is an enzyme hydrolase responsible for removing phosphate groups from various types of molecules such as nucleotides, proteins and alkaloids. This enzyme accordingly allows absorption of nutrients and elimination of metabolites hence generates an inactive, non-toxic form iAP in inflamed mucosa of IBD [14].

In IBD patients, several investigators have analyzed metabolites associated with the inflammation that could serve as biomarkers or specific therapeutic targets. In urine, some metabolites of proteins and CHO have been identified higher levels such as allantoin, tryptophan, lactate and carnitine, this manifestation is attributing to low production of metabolizing enzyme however, CD patients exhibited an increase in sugars, such as xylose, maltose, galactose and lactose compared to the control cohort [15].

Metabolic profiling is a powerful tool to identify intestinal inflammation, to exploring the IBD pathogenesis and may be useful in the management of patients for identify deficiencies, because IBD patients tend to have high protein loss, specific amino acids or oligosaccharide malabsorption due to ulcerations in the
bowl, so protein needs could be higher (1.5 g/kg) [5, 15].

On the other hand, experimental evidence exist that supports the hypothesis that fructooligosaccharides increases the intestinal flora and modulates of chronic intestinal inflammation [16], specifically inulin and oligofructose could prevent or mitigate intestinal inflammatory lesions in human CD, UC and pouchitis [17].

**Probiotics**

The microbiotic play a number of key roles in the maintenance of health, including aiding digestion of otherwise indigestible dietary compounds, synthesis of vitamins and other beneficial metabolites, immune system regulation and enhanced resistance against colonization by pathogenic microorganisms [18]. Abnormal microbiotic composition and decreased complexity of the gut microbial ecosystem are features of CD and UC [19].

Actually exist controversy about effectiveness of probiotics and prebiotics in IBD patients, some studies have indicated that both may modulate the microbiotic, and reduce the likelihood of IBD regression, although so far no evidence sufficient is available to support the use of probiotics in CD [20].

However, in mice with induced CD a specific probiotic (*Lactobacillus fermentum CECT 5716*) could prevent colonic injury, may be due to early immune stimulation, immune regulatory properties or antioxidant abilities. When this probiotic was administered after inflammation, has therapeutic properties in the late phase of colitis, associated with IL-6 [21].

Similarly, Zakostelska et al. provided evidence about another probiotic bacterium (*Lactobacillus casei DN-114 001*) achieved by mechanisms that improve intestinal permeability (IP) and protect the host from induction of intestinal inflammation [22].

IP is another factor involved in inflammation, metabolism and etiopathogenesis of CD and associated with early relapse. Studies on experimental models of colitis have shown that glutamine improves mucosal permeability [23] moreover; a study in patients with CD also showed that glutamine improved the IP and mucosal architecture, suggesting that oral glutamine (0.5 g/kg ideal body weight/day for 2 months) is effective in improving IP in patients with CD [24].

Probiotic treatment or nonpathogenic flora transplantation involve new and promising therapeutic strategies. The colitogenic ability of environment is not limited to intestinal microbiota, nutrition, toxic habits and stress, also influence the onset of inflammation in IBD [25]. In these patients, probiotics influence gene expression, signaling pathways and cell cycle, thus modulates the immune response. In recent years the intestinal ecosystem has emerged as a key therapeutic target to restore homeostasis in IBD patients.

Therefore, using digestive enzymes along with other natural therapies, such as probiotics and glutamine, can be very helpful for patients with IBD. Long term use of these natural products often allows a reduction or elimination in drugs commonly used to treat this widespread condition.

**Fatty Acids (FA)**

Evidence from genetic and immunologic studies suggests that metabolism and inflammation are tightly linked. Microbial lipids, have been demonstrated to play key roles in the regulation of inflammation through different functions (ligands of lipid-activated nuclear receptors, regulators of gene expression, pro or anti-inflammatory mediators, intracellular signaling molecules or antigens); however, it is important to note that there is, new evidence of the role of FA in IBD [26].

Abnormalities of lipid metabolism have been identified in IBD patients active or in remission. Lower unsaturated lipid levels have been reported, probably for altered systemic lipid metabolism related to the chronic inflammation that persists even in quiescent disease. Dietary or pharmaceutical intervention may be indicated to ameliorate the lipid profile in IBD patients and to supplement choline [27].

**1) Monounsaturated Fatty Acids (MUFA)**

In recent studies conclude that the amount and the type of dietary fat as a therapeutic in enteral nutrition. In CD very low fat (<3g/1000 kcal) diets could be particularly effective, and olive oil based diets are better than diets based on seed oils. Therefore, oleic acid would be better than linoleic acid in reducing inflammation [25]. In a mice study,a virgin olive oil diet was protective and preventive of colorectal cancer, and proinflammatory cytokine levels were significantly lower [28].

Some findings demonstrate that MUFA can modulate gene expression with ligands of these fatty
acids; Borniquel et al. showed that administration of nitrate oleic acid attenuates colonic inflammation and improves clinical symptoms in experimental IBD, through of activation of ligands for Peroxisome Proliferator-Activated Receptor γ (PPARγ) expression in colon [29]. Hepatocyte Nuclear Factor-4γ (HNF4γ) is another gene with MUFA ligands and low expression in active UC patients [30, 31].

2) Polyunsaturated Fatty Acids (PUFA)

Arachidonic acid (n-6): This PUFA is present in the phospholipids of membranes of the body’s cells, is involved in cellular signaling as a lipid messenger, and is a precursor for the production of eicosanoids. Genetic studies support a role for arachidonic acid metabolites in IBD [32], but their activity is controversial. Variable results have been reported in terms of its effects on intestinal inflammation [33, 34]. A study in rats suggested that dietary PUFA supplementation, or consumption of foods rich in these compounds, may reduce or prevent IBD symptoms because it causes proteomic changes on interleukin (IL) 10 associated with the reduction in inflammation [35]. Also partial replacement of n-6 diet with medium chain triglycerides (MCT) decreases the incidence of colitis in a model of spontaneous intestinal inflammation [36] accordingly MCT could be a possible adjunctive therapy in CD patients.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (n-3): In vitro EPA and DHA have been able to reduce production of IL-6 and IL-8 through PPARγ in enterocyte. In rats the combination of n-3 and 5-Aminosalicylic Acid (5-ASA) ameliorated inflammatory score in colitis, suggesting dual therapy to reduce dose standard from 75 to 25 mg/kg/day [37].

Therefore, low fat saturated diets have been described as particularly useful to decrease inflammation in IBD patients. Together with lipid sources such as olive oil, medium-chain triglycerides and omega-3 FA might have a therapeutic effect [36, 38].

Both n-3 and n-6, are precursors of potent lipid mediators; play an important role in the regulation of inflammation due to their ability to inhibit the formation of eicosanoids via the cyclooxygenase (COX) and lipoxygenase (leukotrienes) pathways [38, 39]. The

Figure 1: Diagram of proposed mechanisms of (polyunsaturated) FA, whereby these FA are involved in the modulation of immune system functions. FA regulate gene expression via nuclear factor-xB (NFκB) and intracellular signaling pathways. (LOX, lipoxygenase; COX, cyclooxygenase; LTs, leukotrienes; PGs prostaglandins; PPAR, peroxisome proliferator-activated receptor; PLA, enzyme phospholipase).
balance is very important for keep adequate fluidity in cell membranes, because n-6 increased rigidity and n-3 allows greater elasticity, during IBD inflammation this effect could optimize the cellular functions [36]. The summary of some proposed hitherto mechanisms of FA functions are depicted in Figure 1.

CONCLUSIONS

IBD is a disease with epidemiological importance and constantly increasing maybe due increased intake of simple sugars and saturated FA. Intestinal permeability and inflammation may be improved with adjunctive therapies of FA n-3 and n-6. Consumption of probiotics in appropriate stages of the disease and in correct amounts could help improve the symptoms.

REFERENCES


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