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World J Gastroenterol 2007 January 7; 13(1): 1-7
World Journal of Gastroenterology ISSN 1007-9327

EDITORIAL

Nutritional modulation of the inflammatory response in inflammatory bowel disease- From the molecular to the integrative to the clinical

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Received: 2006-07-30 Accepted: 2006-10-05

Abstract

Nutrient deficiencies are common in patients with inflammatory bowel disease (IBD). Both total parenteral and enteral nutrition provide important supportive therapy for IBD patients, but in adults these are not useful for primary therapy. Dietary intervention with omega-3 polyunsaturated fatty acids contained in fish oil may be useful for the care of IBD patients, and recent studies have stressed the role of PPAR on NFκB activity on the potential beneficial effect of dietary lipids on intestinal function.

Key words: Crohn's disease; Ulcerative colitis; Enteral nutrition; Parenteral nutrition; Glutamine; Fiber; Long chain fatty acids

Wild GE, Drozdowski L, Tartaglia C, Clandinin MT, Thomson ABR. Nutritional modulation of the inflammatory response in inflammatory bowel disease- From the molecular to the integrative to the clinical. *World J Gastroenterol* 2007; 13(1): 1-7

http://www.wjgnet.com/1007-9327/13/1.asp

INTRODUCTION

Inflammatory bowel disease (IBD) is a term used to denote inflammation of the gastrointestinal mucosa of unknown etiology. There are a number of hypotheses pertaining to the development and perpetuation of IBD. Three major theories emerge from the literature. The first implicates a persistent intestinal infection[1-3]; the second proposes that IBD is a consequence of a defective mucosal barrier to luminal antigens[4,5]; and the third suggests a dysregulated host immune response to ubiquitous antigens[4,6]. It is believed that IBD has both genetic and environmental components, and is immunologically mediated[4,7-9]. Data from IBD patients concerning cytokine profiles, permeability defects, response to treatment, and natural history of disease all indicate a heterogeneous group of illnesses that fall under the headings of ulcerative colitis (UC) and Crohn's disease (CD). Previous epidemiological data covering diet in UC and CD are conflicting, partly due to this heterogeneity of the diseases, difficulty in obtaining reliable data and publication bias such as negative structures of breastfeeding[10].

NUTRITION IN IBD

Specific antibody isotypes to major milk proteins are found in both UC and CD patients. In CD, the antibodies correlate with disease activity[11]. Although ethnic origin[12], and not the IBD disease state, appears to be the main determinant of lactose intolerance, the avoidance of dairy products by IBD patients is extensive[13]. Lack of breastfeeding in infancy has been associated with CD but not UC. In addition, increased carbohydrate consumption has been documented in CD[14]. Others have alluded to a lack of dietary fiber as a predisposing factor for IBD[15]. The development of UC has also been associated with high intakes of monounsaturated fatty acids (MUFA), n6 polyunsaturated fatty acids (n6 PUFA), sulphur-containing diets and vitamin B6[16].

Deficiencies

IBD is associated with a number of nutritional deficiencies including anemia, hypoalbuminemia, hypomagnesia, hypocalcemia and hypophosphatemia, as well as deficiencies in folic acid, niacin, Vitamins A, B12, C, and D as well as deficiencies of iron, zinc, copper[17]. It is not clear if low levels of micronutrients are one of the results of disease or one of primary importance. Plasma antioxidant concentrations are reduced in IBD patients, particularly those with active disease[18]. Antioxidant activity, assessed by measuring selenium concentrations and erythrocyte

glutathione peroxidase activity, is inversely correlated with inflammatory biomarkers, including TNFα[19]. Hyperhomocysteinemia is more common in patients with IBD, and is associated with reduced serum, concentrations of vitamin B12, folate and B6[20].

Several mechanisms contribute to the malnutrition observed in IBD patients. Firstly, there is a decrease in the oral intake of nutrients because of abdominal pain and anorexia. Secondly, the mucosal inflammation and associated diarrhea leads to a loss of protein, blood, minerals, electrolytes and trace elements. Thirdly, multiple resections or bacterial overgrowth may have an adverse nutritional effect; and lastly, the pharmacological therapies may also lead to malnutrition. For example, sulfasalazine reduces folic acid absorption, and corticosteroids decrease calcium absorption as well as negatively affecting protein metabolism[21]. Alterations in energy metabolism may result in increased resting energy expenditure and lipid oxidation in IBD patients[22,23]. The consequences of malnutrition are numerous, and include reductions in bone mineral density[24], as well as growth retardation and delayed sexual maturity in children[25]. Osteoporosis may also be implicated as a result of proinflammatory cytokine profiles.

Nutritional therapy can take on a number of forms which include Total Parenteral Nutrition (TPN) and Total Enteral Nutrition (TEN). The diets used are elemental, polymeric, and exclusion diets. Elemental diets contain nutrients reduced to their basic components: amino acids for proteins, glucose for carbohydrates, and short-chain triglycerides for fats. Polymeric formulas contain whole proteins for nitrogen, glucose polymers for carbohydrates and long-chain triglycerides for starch or fat, respectively[17].

Total parenteral nutrition (TPN)

The use of TPN for the management of IBD is based on certain theoretical advantages: bowel rest is beneficial because it diminishes motor and transport function of the diseased bowel[26,27]; a decrease in antigenic stimulation will eliminate the immunologic responses to food, especially in the presence of impaired intestinal permeability[28-30]; TPN fosters protein synthesis in the intestine which leads to cell renewal, healing, and reversal of impaired immunocompetence.

Ostro and co-workers[31] demonstrated remission rates of 63% to 89% with TPN in a large retrospective series of CD patients who were refractory to conventional medical management. However, Matuchansky *et al*[32] emphasized that there were high relapse rates (40%-62%) after 2 years. It has been suggested that TPN be used only in a nutritionally supportive role[33,34]. In UC, there is no evidence for better outcome with TPN[35,36]. Although remission rates of 9% to 80% have been reported, TPN given to patients with severe colitis appears to only be beneficial as perioperative nutritional support. In patients with mild disease, TPN is more effective but is not better than steroid therapy, and thus the invasiveness and cost of TPN are unjustified. Any benefits associated with TPN may be due to the administration of nutrients, and not bowel rest, as bowel rest alone has no effect on disease activity[37]. Therefore, although TPN has a role in patients with a non-functioning intestine or the short bowel syndrome due to excessive resections, TPN is of limited use as a primary therapy in IBD. This is not intended to be an extensive review of TPN, but it should be cautioned that even in expert centres, TPN is associated with complications such as sepsis and cholestatic liver disease.

Total enteral nutrition (TEN), elemental and defined formula diets

TEN excludes potential toxic dietary factors and antigenic exposure, since there are only amino acids, glucose or oligosaccharides and low lipid content. TEN is not associated with cholestasis, biliary sludge or gallstone formation, as is seen with TPN. Atrophy of the small intestinal mucosa has been observed in animal models receiving long-term TPN, but this atrophy is prevented with TEN. In addition, a 6-wk TPN treatment in dogs resulted in marked reduction in pancreatic weight, a decrease in small intestinal mass, and a decrease in intestinal disaccharidase activity in dogs[38]. For this reason, TEN is preferable to TPN.

The topic of nutrition in GI disorders occurring in IBD has been reviewed recently[39,40]. When compared to TPN, enteral nutrition yielded similar results of preventing and combating malnutrition[35,36,41]. Although Voitk *et al*[42] proposed that elemental diets may be an effective therapy for IBD, enteral nutrition as a primary therapy has failed to yield consistent results in numerous clinical trials. It is true that a number of trials have shown remission rates in CD patients receiving elemental diets, similar to the rates observed with steroid therapy[43-54]. However, it is noteworthy that significantly better remission rates were observed in patients receiving steroid treatment versus elemental diets when including all the diet group drop outs (i.e., on an intent-to-treat basis). The question remains as to the best way of analyzing the results when a large percentage of patients receiving diet therapy drop out because of unpalatibility or intolerance. Furthermore, some studies have shown no difference with elemental diets when compared to steroid therapy[48,52]. In children, elemental diets were associated with greater linear growth, while in adults these diets preserve nitrogen balance[55,56]. The role of nutritional therapy in the context of pediatric onset illness has been reviewed[57]. Thus, enteral nutrition is easier to use, is less expensive, and is a better alternative to TPN. Unfortunately, its unpalatability limits patient compliance, but with strong encouragement this may be partially overcome.

The fat composition of enteral diets may influence the results which are obtained in the various clinical trials. Elemental diets have a low fat content, while most polymeric diets generally contain more fat including more linoleic acid, which is a precursor for the synthesis of potentially proinflammatory eicosanoids[58].

Defined formula diets are usually more palatable and less expensive than are the elemental diets. While some investigators report no differences between elemental and defined formula diets in patients with acute CD[49,59,60], Giaffer *et al*[61] found elemental diets to be more effective

in active CD. A randomized double-blind trial in Crohn's patients demonstrated that elemental and polymeric (defined) diets, differing only in their source of nitrogen, were equally effective in reducing the Crohn's disease activity index (CDAI), and in inducing clinical remission[62]. Although defined formula diets provide less bowel rest, they have the potential advantage of exposing the GI tract to the usual dietary substrates, which allow thereby for the full expression of intestinal, biliary and pancreatic activity[63]. In animal studies, it has also been observed that luminal nutrition has trophic influences on the gut[64].

Is there a beneficial effect of supplementing polymeric formulas with TGF-β1[65]? In pediatric CD, reductions in proinflammatory cytokine concentrations and mRNA, paired with an up-regulation of TGF-β mRNA, was associated with improved macroscopic and microscopic mucosal inflammation. A meta-analysis and a Cochrane review have demonstrated that in adults, corticosteroids are more effective than enteral diet therapy[48-50]. It is unclear what is the role of nutritional therapy in adults with CD[51-53], although there is some evidence in Japan that enteral nutrition enjoys support as primary therapy[53]. In contrast to the generally agreed role in adults of enteral nutrition being useful to improve the patient's nutritional status as its main benefit, in children with CD enteral nutrition has a much clearer benefit to improve clinical, biochemical and growth parameters[55], and may as well have a steroid sparing effect[56,57].

Glutamine, fiber and fatty acids

Diets high in glutamine, an important source of energy for enterocytes and the preferred fuel of the small intestine[66,67], have been used with variable success. Glutamine probably exerts its trophic effects on the small intestine by increasing protein synthesis, and generating alanine as a substrate for enteric gluconeogenesis[68]. There is evidence that glutamine protects the small intestinal mucosa during critical illness[69,70]. However, oral glutamine supplements do not restore to normal the increased permeability seen in patients with CD, and these supplements do not beneficially affect the patients' CDAI or C-reactive protein (CRP) levels[71]. Similarly, a randomized controlled trial demonstrated that no benefit was associated with the intake of glutamine-enriched polymeric formulas in children with CD[72].

In animal studies, dietary fiber has been implicated in maintaining the integrity of the intestine, and in preventing the bacterial translocation from the gut to the mesenteric lymph nodes[73,74]. Short chain fatty acids (SCFA, C1 to C6 organic fatty acids), are produced by the fermentation of dietary polysaccharides by the normal anaerobic bacteria in the colon. These SCFA are a source of energy for the colonocytes, in addition to their enhancing sodium and water absorption and promoting blood flow[75,76]. Reduced levels of SCFA, particularly butyrate, and a defect in the oxidation of butyrate by colonocytes, have been proposed as a mechanism in the pathogenesis of IBD[77,78]. Evidence to support this hypothesis includes the observation that the oxidation of ^{13}C-labelled butyrate is lower in patients with active UC as compared to healthy controls[79]. However, Simpson and co-workers failed to demonstrate differences between UC patients and controls in the oxidation of rectally administered ^{13}C-labelled butyrate[80].

TPN supplemented with SCFA enhanced functional adaptation to intestinal resection in rats. It remains to be determined if patients with short bowel syndrome may benefit from SCFA[81].

Butyrate (C4 fatty acid) administered to UC patients resulted in remission rates comparable to corticosteroids and mesalamine[82]. In patients with CD, both intestinal biopsies and lamina propria cells cultured with butyrate had significantly reduced levels of inflammatory cytokines (TNF), possibly due to a reduction in NFκB activation and IκB degradation[83].

Eicosanoids are inflammatory mediators, and have been implicated in the pathogenesis of chronic inflammatory lesions in the bowel. Specimens from patients with IBD show increased eicosanoid formation[84]. High dietary intake of omega-6 polyunsaturated fatty acids (PUFAs), which reduces omega-3 intake, may contribute to IBD development[85]. The benefits of fish oil, which contain n3 fatty acids, have been shown in some inflammatory diseases such as psoriasis and rheumatoid arthritis. Epidemiological observations of the low prevalence of IBD in Japanese and Inuit populations consuming high n3 fatty acid fish provided a rationale for the use of n3 fatty acids in IBD. The n3 fatty acids are believed to compete with n6 fatty acids as precursors of eicosanoid synthesis. The n3 products are series 5 leukotrienes, which have less physiological activity than do the arachidonate- derived series 4 counterparts. Thus, fish oil may have an anti-inflammatory effect.

Rats fed with fish oil which had TNBS-induced inflammatory lesions in the bowel showed less prostaglandin- and leukotriene-mediated immune response[86]. Parenteral lipid emulsions enriched with n3 fatty acids reduce diarrhea, attenuate morphological changes, and decrease colonic concentrations of inflammatory mediators in an animal model of acetic acid induced colitis[87].

Loeschke *et al*[88] performed a placebo-controlled trial of n3 fatty acids in the prevention of relapse in UC. Patients in remission who received n3 fatty acids experienced fewer relapses than did those receiving placebo. Unfortunately, the beneficial results of this study did not persist throughout the length of the 2 year study, possibly due to decreased compliance over time. In a multicenter placebo controlled relapse prevention trial, Belluzzi *et al*[89] found a significant reduction in the relapse rate in CD patients given a special formulation designed to allow delayed ileal release of n3 fatty acids. A fish oil diet has been shown to increase eicosapentanoic and docosahexanoic acids in the intestinal mucosal lipids of IBD patients, as well as showing a decrease in arachadonic acid. An increase in the synthesis of leukotriene B5 as well as a 53% decrease of leukotriene B4 was shown in UC patients, whereas the fish oil treatment showed a nonsignificant trend to faster remission[90,91]. Fish oil supplementation results in clinical improvement of active mild to moderate disease, but was not associated with a significant decrease in leukotriene B4 production[84]. Thus, fish oil supplementation of the diet may provide some short-term benefit to patients with CD

or UC. The use of probiotics and prebiotics has received much attention; the interested reader is referred to recent reviews in this area[40].

Fatty acids and gene expression

The effect of fatty acids on gene expression was previously thought to result largely from alterations in membrane phospholipids or eicosanoid production. More recently, the discovery of nuclear receptors; such as peroxisome proliferator-activated receptors (PPARs), and their regulation by fatty acids, has changed this view. PPARs are ligand activated transcription factors that upon heterodimerization with the retinoic X receptor (RXR), recognize PPAR response elements in the promoter regions of various genes, and subsequently affect gene transcription. PPARs bind various ligands including nonsteroidal anti-inflammatory drugs (NSAIDS), thiazolidinediones (antidiabetic agents) as well as PUFAs and their metabolites[92-96]. Several subtypes of the receptor have been identified (α,δ,γ) and these are differentially expressed in a variety of tissues. PPARγ is expressed in intestinal tissue, with the highest abundance detected in the colon[97].

PPARγ has been implicated in the regulation of inflammation, and has become a potential therapeutic target in the treatment of inflammatory disorders, including IBD. It has been suggested that patients with UC have a mucosal deficit in PPARγ that may contribute to the development of their disease. Indeed, analysis of mRNA and protein from colonic biopsies shows reduced PPARγ in UC patients when compared to either Crohn's patients or healthy controls[98].

Using colon cancer lines, it has been shown that PPAR ligands attenuate cytokine gene expression by inhibiting NF-κB via an IκB dependent mechanism[99]. A number of other studies suggest that PPAR activators inhibit COX2 by interference with NF-κB[100-102]. PPARs inhibit the AP-1 signaling pathway[103], and interact with the Jun[104] and STAT signaling pathways[105].

Animal studies support the role of PPAR in intestinal inflammation. Thiazolidinedione ligands for PPAR markedly reduced colonic inflammation in a mouse model of IBD[99]. PPAR+/- and RXR +/- mice display enhanced susceptibility to TNBS-induced colitis[106]. The administration of PPAR and RXR agonists synergistically reduce TNBS-induced colitis, with improved macroscopic and histologic scores, reductions in TNFα and IL-1β mRNA, and decreased NF-κB DNA binding activity.

Although clinical data is limited, the results of an open label study using rosiglitazone, a PPARγ ligand as therapy for UC, showed that 27% of patients achieved remission after 12 wk of therapy[107]. Thus, PPARγ ligands may represent a novel therapy for UC, and double-blind, placebo-controlled, randomized trials are warranted.

Of considerable interest, the ability to modulate PPAR nutritionally has been studied. Dietary PUFA have dramatic effects on gene expression through the regulation of several transcription factors, including PPAR. Fatty acid regulation of PPAR was first noted by Gottlicher *et al*[108]. A diverse array of fatty acids, eicosanoids, and fatty acid metabolites have been shown to activate PPAR[94-96]. Both PPARα and PPARγ bind mono- and polyunsaturated fatty acids at levels, which are found in human serum[95]. Thus, the anti-inflammatory effects of n3 PUFA may involve PPAR and interference with NFκB, rather than simply alterations in eicosanoid synthesis.

Clinical Implications

It is widely accepted that nutritional deficiencies are common in patients with CD and UC, and these need to be anticipated, identified and treated. There are no specific diets which can be recommended for all patients with IBD; diet therapy needs to be individualized. TPN or TEN may be necessary to restore nutritional balance in selected IBD patients with malnutrition, but in adults these interventions do not provide a primary option to modify disease activity. The omega-3 PUFAs contained in fish oil may reduce disease activity in UC and CD when used in the short term in conjunction with standard medical therapy. Their mechanism of action may be to enhance the activity of the nuclear receptors PPAR (peroxisome proliferator-activated receptors) in the intestine, inhibiting the AP-1 signaling pathway and NF-κB, attenuating proinflammatory cytokine gene expression. Future research will focus on the identification and use of specific dietary lipids to reduce intestinal inflammatory activity and to maintain long-term disease remission.

ACKNOWLEDGMENTS

The authors thank Ms. Lori Ingram for her excellent editorial assistance.

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