Nutrients and Gut Health

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Inflammatory bowel diseases (IBD), such as ulcerative colitis, pouchitis and Crohn's disease, are chronic inflammatory disorders caused by increased oxidative and metabolic stress. In the last decade, an increase of the incidence rates in different areas of the world has been reported. This also happened in countries (particularly in Asia) where IBD was previously uncommon. It is unclear if the rise of the incidence in this part of the world is due to improved diagnosis methods or environmental triggers.

The exact etiology of IBD is still not clear, but it seems that a genetic predisposition, an exaggerated immune response to environmental triggers (e.g. nutritional components, infections) and the composition of the intestinal bacteria are involved [1, 2]. None of these alone is sufficient or essential to cause the typical intestinal lesions. In the gut, bacteria, the intestinal barrier and the intestinal immune system are a close entity. It is well known from experimental models that without intestinal bacteria no IBD can develop [3, 4]. The composition of the different bacteria is very important [5]. A reduction of the commensal lactobacilli and bifidobacteria can lead to decreased fermentation of unabsorbed carbohydrates with less production of short-chain fatty acids. Butyrate is an important source of energy for the epithelial cells and is able to downregulate inflammation by decreasing the

production of proinflammatory cytokines [6, 7]. In addition, the production of antimicrobial bacteriocins can be decreased [8].

The intestinal barrier is a functional unit including the epithelial cells, mucus and different secreted substances such as defensins, lysozymes and immunoglobulins (e.g. IgA). These components are important to control the microbial composition in the gut. IgA can bind bacteria and viruses, and the defensins have direct antimicrobial activities against bacteria [9–11].

The innate and acquired intestinal immune systems are able to differentiate between the beneficial and harmful bacteria and are therefore essential for the immune homeostasis in the gut. There is constant crosstalk between the intestinal bacteria and the innate immune system. The information is transmitted through specific pattern-recognition receptors (e.g. NOD- and Toll-like receptors) [12].

Patients with IBD have a loss of tolerance to their own intestinal bacteria. It is known that patients with IBD have a decreased number of beneficial bacteria and an increased number of pathogenic bacteria adherent to the mucosa and within the epithelium [2]. It appears that these bacteria trigger a strong mucosal immunological response leading to inflammation and intestinal epithelial cell injury, mediated by activated T cells, mononucle-

ar cells and macrophages. If this response cannot be downregulated by regulatory T cells, numerous inflammatory cytokines are activated by stimulation of the intercellular transcription factor NF- κ B. It has been shown that bacterial lipopolysaccharides or peptidoglycans can activate NF- κ B by binding to specific pattern recognition receptors [12]. It is still unknown why the proinflammatory response cannot be downregulated and why the inflammatory drive continuously leads to mucosal damage resulting either in Crohn's disease or ulcerative colitis.

In the whole process of inducing or prolonging inflammatory process, it seems possible that nutritional components can be involved. It is well known that the specific metabolites from nutrients can change the composition of the intestinal bacteria. This can be involved in the pathogenesis of IBD, and can also help treat or prolong remission in IBD.

The article by Ioannidis et al. [13] in this issue of *Digestion* describes several possible mechanisms of different nutrients which can be involved. Specific nutrients are able to regulate the intestinal bacteria, sequester intraluminal antigens, modulate the immune response, increase the antioxidant status, stimulate production of short-chain fatty acids and regulate intestinal motility. The balance between oxidative and antioxidative agents is crucial for the immune functions of cells because it preserves the integrity and function of the cellular membrane, cellular proteins and nucleic acids as well as controls intracellular signaling and gene expression [14]. Among the antioxidants, glutathione is very important. There is evidence that oxidative stress promotes cellular apoptosis and that antioxidants could have a protective role. Although there are candidates of nutritional additives, such as selenium, glutamine or cysteine, which can increase glutathione levels, there are no good clinical data to prove this concept. The same is true for other antioxidants such as vitamins (A, C, E).

Different lipids are very important. Dietary lipids induce changes in cell membrane phospholipids, which, in response to an inflammatory trigger, synthesize eicosanoids with different degrees of pro- or anti-inflammatory activities through up- or downregulation of the expression of pro- or anti-inflammatory cytokines and adhesion molecules [15]. Several lipid compositions in diets were studied in Crohn's disease, but the results are still controversial. Enteral diets with a low content of long-chain triglycerides, or in diets where part of the long-chain triglycerides were replaced with medium-chain triglycerides, did not achieve clear beneficial effects [16]. In a Cochrane analysis, no clear benefit could be demon-

strated for low-fat diets compared to high-fat diets [17]. Different types of long-chain triglycerides were compared: one was high in oleate and the other was high in linoleate in patients with active Crohn's disease. The remission rates with linoleate were significantly higher than with oleate [18]. The effect of n-3 fatty acids (e.g. fish oil) on the inflammatory response was studied in Crohn's disease and ulcerative colitis. The reported effect showed mixed results. A systemic review of 13 controlled trials showed that fewer than 6 were identified that assessed the effects of n-3 fatty acids on single outcome parameters. In 3 studies, a reduction of corticosteroid requirements was found, although statistical significance was shown in only one of these studies.

At present, it is not possible to draw a clear conclusion regarding the effects of n-3 fatty acids on clinical, endoscopic and histological scores, or on remission and relapse rates [19]. The effects of different types of lipids on inflammatory activity deserve further studies. Furthermore, after an initial study showing great benefits of diet supplementation with n-3 fatty acids containing enteric-coated capsules in Crohn's disease, there was a great hope to reduce relapses [20]. These beneficial effects, however, could not be reproduced in 2 large, recently published studies [21].

In the last decade, there was much hope that different fiber (prebiotics) and probiotics could be a corner stone in modulating the immune response in IBD patients. Prebiotics are soluble poly- or oligosaccharides (inulin, pectin, fructo- and galacto-oligosaccharides) and serve in the intestine as substrates for fermentation [22]. Probiotics are nonpathogenic bacteria which are able to exert positive health benefits in the gastrointestinal tract. They are able to adhere to the intestinal mucosa and can stimulate the secretion of IgA and mucus production. They may reduce the levels of proinflammatory cytokines (TNF- α , IL-1, IL-6) and increase levels of anti-inflammatory cytokines (IL-10, TGF- β). Furthermore, they can induce defensin secretion and increase heat shock proteins [23–26].

Pre- and probiotics can interact with the commensal intestinal bacteria and may therefore influence the intestinal ecosystem. This effect is eminent in the colon, where anaerobic bacteria can ferment nonabsorbable dietary carbohydrates. Through fermentation, the intestinal pH decreases, which stimulates the growth of nonpathogenic bacteria (prebiotic effect) and liberates short-chain fatty acids. Butyrate prevents the expression of specific genes and coding cytokines from intensifying the inflammatory response. In addition, butyrate increases apoptosis of inflammatory cells [27, 28].

So far, the use of pre- and probiotics was found to be more beneficial in ulcerative colitis than in Crohn's disease. The use of fermentable fiber supplementation achieved similar remission rates in ulcerative colitis as mesalazine [29]. In several studies, administration of *Escherichia coli* Nissle 1917 and *Lactobacillus* GG was compared with mesalazine in ulcerative colitis. In these studies, probiotics maintained remission at similar rates as mesalazine [30–32]. Good clinical results were also published using probiotics in patients with pouchitis. A combination of eight different bacteria compared to placebo showed that relapses of pouchitis and the development of pouchitis after surgery could be reduced [33, 34]. The article by Ioannidis et al. [13] describes the different

possible nutrition-derived mechanisms involved in the pathogenesis of IBD well. In addition, it offers an excellent summary of the possible preventive and treatment options using different nutrients in IBD patients.

Although there are many good studies in cell culture and in animals using specific nutrients, there are still a lot of unanswered questions. I am sure that continuing research will show us that we can partially change the history of IBD by using specific nutrients in the future. The most promising substrates are nutritional additives, which can change the composition of the intestinal bacteria. There is still a lot of work to be done. The above-mentioned article is very interesting and important for scientists and practitioners interested in IBD.

References

- Podolsky DK: Inflammatory bowel disease. *N Engl J Med* 2002;347:417–429.
- Swidsinsky A, Ladoff A, Pernthaler A, et al: Mucosal flora in inflammatory bowel disease. *Gastroenterology* 2002;122:44–54.
- Kuhn R, Lohler J, Rennick D, Rajewsky K, Muller W: Interleukin-10-deficient mice develop chronic enterocolitis. *Cell* 1993;75:263–274.
- Sadlack B, Merz H, Schorle H, Schimpl A, Feller AC, Horak I: Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene. *Cell* 1993;75:253–261.
- Madsen KL, Doyle JS, Jewell LD, et al: Lactobacillus species prevents colitis in interleukin 10 gene-deficient mice. *Gastroenterology* 1999;116:1107–1114.
- Segain JP, Raingeard de la Bltire D, Bourreille A, et al: Butyrate inhibits inflammatory responses through NFkappaB inhibition: implications for Crohn's disease. *Gut* 2000;47:397–403.
- Venkatraman A, Ramakrishna BS, Shaji RV, Kumar NS, Pulimood A, Patra S: Amelioration of dextran sulfate colitis by butyrate: role of heat shock protein 70 and NF-kappaB. *Am J Physiol Gastrointest Liver Physiol* 2003;285:G177–G184.
- Corr SC, Li Y, Riedel CU, et al: Bacteriocin production as a mechanism for the anti-infective activity of *Lactobacillus salivarius* UCC118. *Proc Natl Acad Sci USA* 2007;104:7617–7621.
- Meyer-Hoffert U, et al: Secreted enteric antimicrobial activity localises to the mucus surface layer. *Gut* 2008;57:764–771.
- Wehkamp J, et al: Defensin deficiency, intestinal microbes, and the clinical phenotypes of Crohn's disease. *J Leukoc Biol* 2005;77:460–465.
- Lehrer IR, et al: Defensins: antimicrobial and cytotoxic peptides of mammalian cells. *Annu Rev Immunol* 1993;11:105–128.
- Sartor RB: Induction of mucosal immune responses by bacteria and bacterial components. *Curr Opin Gastroenterol* 2001;17:555–561.
- Ioannidis O, Varnalidis I, Paraskevas G, Botsios D: Nutritional modulation of the inflammatory bowel response. *Digestion* 2011;84:89–101.
- Knight JA: Review: free radicals, antioxidants, and the immune system. *Ann Clin Lab Sci* 2000;30:145–158.
- Gassull MA: Review article: the role of nutrition in the treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 2004;20(suppl 4):79–83.
- Sakura T, Matsui T, Yao T, et al: Short-term efficacy of enteral nutrition in the treatment of active Crohn's disease: a randomized, controlled trial comparing nutrient formulas. *J Parenter Enteral Nutr* 2002;6:98–103.
- Zacos M, Tondeur M, Griffiths AM: Enteral nutritional therapy for inducing remission of Crohn's disease. *Cochrane Database Syst Rev* 2001;3:CD000542.
- Khoshoo V, Reifen R, Neuman MG, Griffiths A, Pencharz PB: Effect of low- and high-fat, peptide-based diets on body composition and disease activity in adolescents with active Crohn's disease. *J Parenter Enteral Nutr* 1996;20:401–405.
- MacLean CH, Mojica WA, Newberry SJ, et al: Systematic review of the effects of n-3 fatty acids in inflammatory bowel disease. *Am J Clin Nutr* 2005;82:611–619.
- Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, Miglioli M: Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N Engl J Med* 1996;334:1557–1560.
- Feagan BG, Sandborn WJ, Mittmann U, et al: Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. *JAMA* 2008;299:1690–1697.
- Hammes WP, Hertel C: Research approaches for pre- and probiotics: challenges and outlook. *Food Res Int* 2002;35:165–170.
- Johansson ML, Molin G, Jeppsson B, Nobaek S, Ahrn S, Bengmark S: Administration of different *Lactobacillus* strains in fermented oatmeal soup: in vivo colonization of human intestinal mucosa and effect on the indigenous flora. *Appl Environ Microbiol* 1993;59:15–20.
- Molin G, Jeppsson B, Johansson ML, et al: Numerical taxonomy of *Lactobacillus* spp. associated with healthy and diseased mucosa of the human intestines. *J Appl Bacteriol* 1993;74:314–323.
- Schiffrin EJ, Rochat F, Link-Amster H, Aeschlimann JM, Donnet-Hughes A: Immunomodulation of human blood cells following the ingestion of lactic acid bacteria. *J Dairy Sci* 1995;78:491–497.
- Link-Amster H, Rochat F, Saudan KY, Mignot O, Aeschlimann JM: Modulation of a specific humoral immune response and changes in intestinal flora mediated through fermented milk intake. *FEMS Immunol Med Microbiol* 1994;10:55–63.
- Inan MS, Rasoulpour RJ, Yin L, Hubbard AK, Rosenberg DW, Giardina C: The luminal short-chain fatty acid butyrate modulates NF-kappaB activity in a human colonic epithelial cell line. *Gastroenterology* 2000;118:724–734.

- 28 Lévy P, Robin H, Bertrand F, Kornprobst M, Capeau J: Butyrate-treated colonic Caco-2 cells exhibit defective integrin-mediated signaling together with increased apoptosis and differentiation. *J Cell Physiol* 2003;197:336–347.
- 29 Fernández-Bañares F, Hinojosa J, Sánchez-Lombrana JL, et al: Randomized clinical trial of *Plantago ovata* seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. Spanish Group for the Study of Crohn's Disease and Ulcerative Colitis (GETECCU). *Am J Gastroenterol* 1999;94:427–433.
- 30 Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT: Non-pathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* 1999;354:635–639.
- 31 Kruis W, Frick P, Pokrotnieks J, et al: Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. *Gut* 2004;53:1617–1623.
- 32 Zocco MA, dal Verme LZ, Cremonini F, et al: Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* 2006;23:1567–1574.
- 33 Gionchetti P, Rizzello F, Venturi A, et al: Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;119:305–309.
- 34 Gionchetti P, Rizzello F, Helwig U, et al: Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology* 2003;124:1202–1209.