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Food and Intestinal Microorganisms: Factors in Pathogenesis, Prevention and Therapy of Ulcerative Colitis

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1. Introduction

Ulcerative colitis (UC) is a chronic and relapsing inflammatory disease of the large bowel characterized by dysregulation of the immune mucosal response, an imbalance in the synthesis and release of cytokines, and an unresolved inflammatory process associated with mucosal damage (Schirbel & Fiocchi, 2010).

Although the exact mechanisms of the development of UC have not been established yet, it is known that both genetic predisposition and environmental factors are playing important roles. There is the strong evidence that environmental factors are involved in the pathogenesis of UC. The incidence of UC has increased dramatically between 1940s and the 1980s. More recent data show that, in several developed countries, UC incidence decreases in the last years (Binder, 2004). On the other hand, at the same time, the incidence of UC increased in countries where it formally was low (e.g. developing countries and developed countries in Asia, such as Japan and Korea). It is believed that factors associated with 'Westernization' may be conditioning the expression of UC. The increased incidence of UC among migrants from the low-incidence to high-incidence areas within the same or next generation confirms a strong environmental influence (Bernstein & Shanahan, 2008).

Another evidence for the role of environmental factors in UC comes from twin studies: disease concordance in monozygotic twins is only 19% in UC, as opposed to 50% in Crohn's disease (CD). This observation suggests that the environmental influence is stronger in UC than in CD (Halfvarson et al., 2003).

In the last decades several environmental factors, and especially the diet and the changes of the gut microbiota have been studied to improve our understanding of increased incidence of inflammatory bowel disease (IBD) in the last years and also to elucidate the pathogenesis of the disease.

2. Diet as a risk factor for the development of ulcerative colitis

The evidence about the role of dietary factors in UC etiology is relatively scarce. However, over the past few decades, several studies have highlighted the potential association between diet and the risk of UC.

Some studies have shown that breastfeeding reduces the risk of development of UC (Corrao et al., 1998) and CD (Koletzko et al., 1989). There are also some studies which could not confirm the positive association between breastfeeding and subsequent development of UC (Koletzko et al., 1989). In 2004, a systematic review and meta-analysis reported a significant protective effect of breastfeeding against both CD and UC (Klement et al., 2004). The role of breastfeeding in the development of childhood onset IBD (<16 years of age) was assessed in the meta-analysis by Barclay et al. Breast milk exposure had a significant protective effect (OR, 0.69; 95% CI, 0.51-0.94; P=0.02) in a developing childhood onset IBD (Barclay et al., 2009). However, the quality of existing data from the included studies was poor, therefore, the role of breastfeeding as a protective factor in developing IBD needs to be investigated in well-designed prospective studies.

In the developed countries with high incidence of IBD, »western lifestyle« includes new feeding habits in which the consumption of high quantities of refined sugar, fat, red meat and the low consumption of dietary fiber, fruit and vegetables take precedence.

In patients with IBD, many studies on sucrose consumption have been conducted since Martini et al. reported in 1976 that patients with CD consumed an excess amount of sugar- and sugar-containing products (Martini et al., 1976). Some other studies have confirmed that ingestion of large amount of refined sugars may be a possible risk factor in the development of IBD (Persson et al., 1992; Reif et al., 1997). The proposed mechanism is the influence of sugars on the composition of intestinal microbiota. In a case control study by Russel et al. the consumption of cola drinks and chocolate consumption were positively associated with developing ulcerative colitis (Russel et al., 1998). A multicenter Japanese study showed that a higher consumption of sweets was positively associated with UC risk and that the intake of vitamin C was negatively related to UC risk (Sakamoto et al., 2005). However, some other studies on the role of refined sugars in the etiology of UC did not confirm the association between the intake of higher amount of refined sugars and development of UC. Therefore, larger prospective studies are needed to elucidate the role of refined sugars in the etiology of IBD.

Several studies reported that the high intake of fats was associated with an increased risk of UC. In a study by Geerling et al. high intakes of monounsaturated and polyunsaturated fat were associated with an increased risk to develop UC (Geerling et al., 2000).

The large European Prospective Investigation into Cancer and Nutrition (EPIC) study from over 200,000 subjects across five European countries assessed dietary data in subjects who were diagnosed with UC compared to control subjects. The study showed a significant positive correlation between the dietary content of linoleic acid (omega-6-fatty acid) and increased incidence of UC, and a negative association with intake of docosahexaenoic acid (omega-3-fatty acid) (Tjonneland et al., 2009).

In a recent British study investigating the total dietary intake of omega-3 polyunsaturated fatty acids (PUFAs) and the specific omega-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on the risk of developing incident UC, the total dietary omega-3 PUFAs, EPA, and DHA were associated with protection from UC in a large cohort of subjects aged over 45 years. Authors concluded that increasing the population's intake of omega-3 PUFAs from oily fish may help prevent UC (John et al., 2010).

Hou et al. performed a systematic review of possible association between pre-diagnosis dietary intake and risk of developing IBD and have identified 19 studies (18 case-control and one cohort) with 2,609 IBD patients (1,269 CD and 1,340 UC and over 4,000 controls). Studies reported that high intakes of total fats, PUFAs, omega-6 PUFAs, and meat were

consistently associated with increased risk of developing UC as well as CD. High vegetable intake was associated with decreased risk of developing UC, whereas fiber and fruit intake was associated with reduced risk of CD (Hou et al., 2011). However, this systematic review is affected by the limitations of the individual studies and potential publication bias against negative studies. Furthermore, studies are heterogeneous in study design, nutrient cut-offs and study populations. The retrospective nature of the majority of studies may have resulted in recall bias involving IBD cases. Therefore, further prospective studies will be needed to elucidate the association between dietary factors and the risk of UC as well as CD.

3. The role of nutrition in the therapy of ulcerative colitis

Inflammatory bowel disease is frequently associated with nutritional deficiencies in calories, macro- and micro-nutrients. Malnutrition is common in active CD, however, nutritional deficiencies can develop fast also in UC patients, especially during periods of active disease. The pattern and severity of nutritional deficiencies depends on the extent, activity and duration of the inflammation (Lucendo & De Rezende, 2009). Nutritional deficiencies are especially common in both pediatric CD and UC, therefore, the nutritional support is especially important in childhood IBD. Providing macronutrients can improve growth. Identifying and correcting micronutrient deficiencies can improve comorbid conditions like osteopenia and anemia (Mallon & Suskind, 2010). Malnutrition and specific deficits, e.g. of iron, zinc, selenium, water and lipid soluble vitamins, are a consequence of several mechanisms: apetite loss, increased energy consumption, malabsorption, intestinal losses, changes in metabolism due to systemic inflammatory cytokine effects and drug therapy. Therefore, the main purpose of nutritional treatment of IBD is to provide adequate intake of all macro- and micronutrients to compensate for existing deficiencies and to cope with increased demands. Specialized nutritional formulas for IBD patients are produced that ensure adequate and complete intake of all necessary nutrients. Exclusive enteral nutrition (EN) is an established primary therapy for pediatric CD and allows the inflammatory activity to be controlled and kept in remission, however enteral nutrition does not have a primary role in the therapy of ulcerative colitis (Otley et al., 2010).

Nutritional support in IBD is frequently used to treat malnutrition, however there is also an attempt to modulate intestinal inflammation. Nutrients may be involved in the modulation of the immune response as components of cell membranes, they can also mediate the expression of proteins involved in the immune response, especially the cytokines and adhesion molecules. Immunologic mechanisms have been also postulated to link food antigens and the development of intestinal inflammation (Torres & Ríos, 2008).

The emerging concepts of nutrition-gene interaction gave birth to unique scientific fields, nutrigenetics and nutrigenomics. These studies provide information about the genetic variability that induces an individual's response to nutrition and changes in gene expression that develop as a result of food-gene interaction. In IBD, the role of diet in the regulation of the immune response to gut microbiota is the subject of current intensive evaluation. These approaches may lead clinicians to derive a personalized nutritional prescription based on individual genetic variations and may result in a significant impact on IBD treatment (Ferguson, 2010).

Intestinal immune responses could be modulated by supplementation with specific immunomodulatory amino acids. Experimental studies evaluating glutamine, the preferential substrate for enterocytes, are promising. The role of arginine, involved in nitric

oxide and polyamines synthesis, still remains debated. However, the effects of these amino acids and other candidates like glycine, cysteine, histidine, or taurine should be evaluated in the future (Coëffier et al., 2010).

3.1 The role of fats in ulcerative colitis

Many studies have confirmed the important role of lipids in the diet to regulate inflammatory processes in different diseases, as they are the fundamental component of cell membranes, including those of lymphocytes and other immune cells, which orchestrate immune system responses (Ioannidis et al., 2011). Some studies have shown that high-fat diets have been associated with an imbalance between effector T cells and regulatory T cells and therefore with increased risk for UC what was confirmed in mouse models of experimental colitis. Mice receiving the high-fat diet were more susceptible to experimental-induced colitis compared to mice fed a normal diet (Jeffery et al., 1997).

The observation that the Eskimos in Greenland, consumers of large quantities of omega-3 PUFAs deriving from fish oils, had a low prevalence of IBD, led to the study of the anti-inflammatory properties of omega-3 PUFAs in comparison with pro-inflammatory omega-6 PUFAs (Bang et al., 1980).

Polyunsaturated fatty acids are involved in the immune response as they are precursors of the eicosanoids. Omega-3 PUFAs are considered to have a beneficial effect in the management of IBD by repressing cytokine production and modulating the production of eicosanoids. Omega-3 PUFAs compete with omega-6 PUFAs in the substrate pool of the lipooxygenase pathway, thus reducing the production of inflammatory eicosanoids like leukotriene B_4 (LTB_4) and thromboxane A_2. They cause a shift from LTB_4 to LTB_5 production which is less bioactive (Calder, 2009).

All the mechanisms through which the omega-3 PUFAs perform their immunomodulating action still remain unclear. Changing the fatty acid composition of immune cells also affects T cell reactivity and antigen presentation. Fatty acids can also influence cytokine (TNF-alfa, IL-1) production. To a certain extent this action may be due to the altered profile of regulatory eicosanoids, but it seems likely that eicosanoid-independent actions are a more important mechanisms. Indeed, effects on transcription factors that regulate inflammatory gene expression (e.g. nuclear factor kappaB) seem to be important (Galli & Calder, 2009). Recently, Vieira de Barros et al. demonstrated that the soybean (source of omega-6 PUFAs) and fish oil (source of omega-3 PUFAs) mixture, more than fish oil alone, increased IL-10/IL-4 ratio (anti-inflammatory/pro-inflammatory) in experimental dextran sodium sulphate-induced colitis rats to levels closer to the control group of non-colitis rats (Vieira de Barros et al., 2011). This finding shows that a balanced omega-3/omega-6 diet may be a key factor which could exert beneficial effects in UC. Indeed, many current »Western diets« provide a high omega-6/omega-3 ratio of over 15:1 and it is recommended that human diet should return to a more balanced omega-6/omega-3 ratio of around 1:4 or less.

Dietary fatty acids are also important risk factors in carcinogenesis due to their lipid peroxidation products. The omega-6 PUFAs have been considered to increase lipid peroxidation via cyclooxygenases, while omega-3 PUFAs exerts a chemopreventive role by suppressing the formation of lipid peroxidation products derived from arachidonic acid oxidation through competitive inhibition of desaturases (Rose & Connolly, 1999). It is well known that patients with UC have increased risk of developing colorectal cancer (CRC), therefore, the consumption of appropriate amount of omega-3 PUFAs may be beneficial in the prevention of CRC.

Although fish oil supplementation in patients with IBD results in omega-3 PUFAs incorporation into gut mucosal tissue and modification of inflammatory mediator profiles, the evidence of clinical benefits of omega-3 PUFAs is conflicting. Some studies have demonstrated the efficacy of fish oil and omega-3 PUFAs in the management of UC (Hawthorne et al., 1992; Stenson et al., 1992), however, a meta-analysis performed by Turner et al. in 2007 found no evidence that supports the use of omega-3 PUFAs (fish oil) for maintenance of remission in UC (Turner et al., 2007).
In a recent systematic review and meta-analysis of the efficacy and safety of omega-3 PUFAs (and fish oil) for maintaining remission in CD and UC, the same authors came to the same conclusion. Nine studies were eligible for inclusion; six studies of 1039 CD patients and three studies of 138 UC patients. For UC, there was no difference in the relapse rate between the omega-3 and control groups (RR 1.02; 95% CI: 0.51-2.03). Additionally, the analysis showed a higher rate of diarrhea and symptoms of the upper gastrointestinal tract in the omega-3 treatment group. The authors concluded that there were insufficient data to recommend the use of omega 3 PUFAs for maintenance of remission in CD and UC (Turner et al., 2011).

3.2 The role of short-chain fatty acids in ulcerative colitis

The multiple beneficial effects on human health of the short-chain fatty acids (SCFA) are well documented. SCFAs are organic acids produced by intestinal microbial fermentation of mainly undigested dietary carbohydrates, specifically resistant starches and dietary fiber, but also in a minor part by dietary and endogenous proteins. SCFAs are essentially produced in the colon. The ratio of SCFA concentrations in the colonic lumen is about 60% acetate, 25% propionate, and 15% butyrate. As a result of increasing concentrations of acidic fermentation products, the luminal pH in the proximal colon is lower. The ability to produce butyrate is widely distributed among the Gram-positive anaerobic bacteria that inhabit the human colon. Numerically, two of the most important groups of butyrate producers appear to be *Faecalibacterium prausnitzii,* which belongs to the *Clostridium leptum* (or clostridial cluster IV) cluster, and *Eubacterium rectale/Roseburia spp.*, which belong to the *Clostridium coccoides* (or clostridial cluster XIVa) cluster of firmicute bacteria (Canani et al., 2011).
Short-chain fatty acids and, especially, butyrate play a very important role in the biology of the large bowel epithelium, representing the primary energy source of the large bowel cell. They have been proposed to play a key role in the maintenance of colonic homeostasis. Deficiency of SCFA in the intestinal lumen is related with epithelium atrophy and inflammation. Butyrate has a role as an anti-inflammatory agent, primarily via inhibition of nuclear factor κB (NF-κB) activation in human colonic epithelial cells. NF-κB regulates many cellular genes involved in early immune inflammatory responses, including IL-1b, TNF-α, IL-2, IL-6, IL-8, IL-12, intercellular adhesion molecule-1 (ICAM-1), T cell receptor-α (TCR-α), and MHC class II molecules. It is well known that the activity of NF-κB is dysregulated in inflammatory bowel diseases (Guilloteau et al., 2011).
Short-chain fatty acids have potent effects on a variety of colonic mucosal functions such as inhibition of carcinogenesis and reinforcing various components of the colonic defence barrier and decreasing oxidative stress. Butyrat is also a potential promoter of the proliferation and differentiation of large intestine epithelial cells and reduces the paracellular permeability, possibly due to the promotion of intestinal cell differentiation. At the intestinal level, butyrate plays a regulatory role on the transepithelial fluid transport and modulates visceral sensitivity and intestinal motility. In vivo studies have shown that butyrate has the pro-absorptive and anti-secretory effect in the distal colon. The mechanisms

of action of butyrate are different; many of these are related to its potent regulatory effects on gene expression (Kovarik et al., 2011).
Several studies have reported that butyrate metabolism is impaired in intestinal mucosa of patients with IBD (Hamer et al., 2008). In UC butyrate oxidation has been shown to be disturbed, but it remains unclear whether this is a primary defect (De Preter et al., 2009). Recently some in vivo studies using biopsy specimens of inflamed mucosa have shown the impaired anti-inflammatory efficacy of n-butyrate in patients with IBD. There is a reduction of butyrate uptake by the inflamed mucosa. The concomitant induction of the glucose transporter GLUT1 suggests that inflammation could induce a metabolic switch from butyrate to glucose oxidation. Butyrate transport deficiency is expected to have clinical consequences. Particularly, the reduction of the intracellular availability of butyrate in colonocytes may decrease its protective effects toward cancer in IBD patients (Canani et al., 2011).
Considering the various beneficial effects of butyrate, it is expected that the administration of butyrate could alleviate the symptoms associated with intestinal inflammation in IBD. The addition of butyrat to standard mesalazine treatment in patients with UC has led to marked improvement of symptoms and endoscopic appearance of mucosa, thus proving effective in reducing disease activity (Assisi et al., 2008). In an Italian double blind, placebo-controlled multicenter trial, 51 patients with active distal UC were treated with rectal enemas containing either 5-aminosalicylic acid (5-ASA) or 5-ASA plus sodium butyrate (80 mmol/L, twice a day). The combined treatment with topical 5-ASA plus sodium butyrate significantly improved the disease activity score more than 5-ASA alone (Vernia et al., 2003). In a study by Hallert et al. an addition of 60 g oat bran (corresponding to 20 g dietary fiber) to the daily diet of patients with quiescent UC resulted in a significant increase of fecal butyrate concentration and in a significant improvement of abdominal symptoms (Hallert et al., 2003). On the other hand, in a recent study by Hamer et al. only minor effects on inflammatory and oxidative stress parameters were observed in UC patients in remission who were treated with rectal butyrate enemas (Hamer et al., 2010).
Although most studies point towards beneficial effects of butyrate, more human in vivo studies are needed to contribute to our current understanding of butyrate-mediated effects on colonic function and its clinical efficacy in reducing inflammation in UC.

4. The role of microbiota in the pathogenesis of ulcerative colitis

Most recent theories regard IBD as a consequence of abnormal mucosal immune response to antigens of gut bacterial microbiota in genetically susceptible individuals.
Previous studies have focused on identifying specific pathogenic microorganisms responsible for IBD. However, further studies have not confirmed the role of specific infectious agents in the pathogenesis of IBD. Moreover, there is growing evidence that the normal bacterial microbiota can trigger harmful immune reactions in susceptible hosts. The most convincing evidence supporting the role of enteric microbiota in the pathogenesis of IBD comes from animal studies. Animals with genetically engineered dysregulation of the immune response developed spontaneous colitis, when they were growing in the normal conditions resembling IBD in humans. However, they did not develop intestinal inflammation when they were growing in a germ free environment indicating that bacterial exposure and colonization of the gut are essential for the development of colitis (Sellon et al., 1998). Interleukin-10 (IL-10) deficient mice displayed a significantly higher number of mucosal adherent bacteria and lower level of protective bacteria like *Lactobacillus* compared to healthy mice. The proportion of mucosal adherent bacteria and the development of colitis

were significantly decreased by nutritional supplementation of lactose or enema delivery of *Lactobacillus reuteri* (Madsen et al., 1999). Similarly, *Lactobacillus plantarum* attenuated established colonic inflammation in IL-10 deficient mice as was manifested by decreased histological colitis score and mucosal cytokines IL-12, interferon gamma (IFN-gamma) and immunoglobulin G2a level (Schultz et al., 2002).

Several studies in humans have observed the role of gut microbiota in the pathogenesis of IBD. The inflammation of gut mucosa and consequent lesions occur predominantly in the areas with the highest bacterial counts like terminal ileum and colon (Sartor, 1997). Rutgeerts et al. reported that the recurrence of mucosal inflammation in the neoterminal ileum after curative ileal resection in patients with IBD was dependent on the fecal stream. The relapse of the inflammation occurred after the restoration of the fecal stream (Rutgeerts et al., 1991). In a study by D'Haens et al. early IBD lesions were induced in susceptible individuals by the direct installation of fecal material into non-inflamed loops of the intestine (D'Haens et al., (1998).

Human studies have repeatedly shown that microbiota of patients with IBD differs from that of controls and is unstable, both in the intestinal lumen and on the surface of the mucosa (Chassaing et al., 2011). A single pathogen has not been identified, but potentially pro-inflammatory micro-organisms have been found in the mucosal samples from IBD patients more often than from healthy controls. Shifts in the composition of resident bacteria in CD and UC patients have been postulated to drive the chronic inflammation seen in both diseases (the »dysbiosis hypothesis«) (Marteau, 2009).

The gut microbiota composition in IBD shows a decreased prevalence of dominant members of the human commensal microbiota (*Bifidobacterium* and *Lactobacillus* species, *Clostridium* IXa and IV groups) and a concomitant increase in detrimental bacteria (sulphate-reducing bacteria, adherent/invasive *Escherichia coli*) (Fava& Danese, 2011).

Considering the important role of intestinal microbiota in the development and maintenance of intestinal inflammation in IBD, many efforts have been made to find ways to influence on bacterial composition in a way to decrease inflammation and prevent exacerbations. With this intention, pre- and probiotis are increasingly used (Sartor, 2004).

5. The role of prebiotics in ulcerative colitis

Prebiotics are defined as nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth or activity of one or a limited number of bacterial species already resident in the colon. Therefore, the rationale behind prebiotic use is to increase the populations of certain endogenic beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*. This change may act beneficially by causing luminal production of SCFA, which induce acidic environment, by preventing of pathogenic bacteria adherence and by production of anti-bacterial substances (Roberfroid et al., 2010).

Prebiotics are usually in the form of oligosaccharides, which may occur naturally but can also be added as dietary supplements to foods, beverages, and infant formula. Prebiotic oligosaccharides often contain fructose chains with a terminal glucose and typically consist of 10 or fewer sugar molecules. Examples of prebiotic oligosaccharides include fructooligosaccharides (FOS), galactooligosaccharides (GOS) and inulin. Inulin and FOS are composed of multiple saccharide units, which are indigestible by the human enzymes. They stimulate the growth of lactic acid bacteria and the generation of SCFA (Thomas & Greer, 2010).

Although several prebiotic compounds possess promising properties to have beneficial effect in IBD, only few of them have been clinically tested.
In dextran sodium sulphate (DSS) - induced colitis of an animal model, inulin attenuated gut inflammation (Videla et al., 2001). Similarly, FOS were shown to decrease the severity of damage of the intestinal mucosa in the experimental model of rat colitis (Cherbut et al., (2003). Psyllium, also called Ispaghula husk or Plantago ovata, is a water soluble dietary fiber. Hallert et al. reported that Ispaghula husk had significantly attenuated symptoms in patients with UC (Hallert et al., 1991) and Spanish Group for the Study of Crohn's Disease and Ulcerative Colitis (GETECCU) found it as efficient as sulfasalazine in maintaining remission in UC (Fernandez-Banares et al., 1999).
Germinated barley foodstuff (GBF) is derived from aleurone layer and scutellum fractions of germinated barley and consists mainly of dietary fiber and glutamine-rich protein. It induces intestinal microflora to produce SCFA (Kanauchi et al., 1999). Treatment of rat experimental colitis with GBF led to improvement of the clinical and pathological signs of colitis and decreased serum cytokine production (Kanauchi et al., 2003). The same Japanese group reported the efficacy of GBF in some studies in patients with active UC and UC in remission (Kanauchi et al., 2003; Hanai et al., 2004). According to these results, GBF has been registered as a special foodstuff for UC by Japan's Ministry of Health, Labor and Welfare.
Given the important influences on intestinal microbiota and immune functions, prebiotics are considered as a promising tool in the management and prevention of IBD in the future. However, larger and well-designed clinical studies are necessary to elucidate the efficacy of prebiotics in patients with UC.

6. The role of probiotics in ulcerative colitis

Probiotics are defined as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. Multiple mechanisms of action have been suggested to explain the effect of probiotics in IBD. These mechanisms include suppression of growth, epithelial binding and invasion by pathogenic bacteria, production of antimicrobial substances, improved epithelial barrier function, and immunoregulation (Collado et al., 2009).
A large body of data is showing a great potential of probiotic use in the treatment of IBD patients. The effects of probiotics are both strain- and dose - dependent. For example, the probiotic *Lactobacillus rhamnosus* GG (LGG) attenuated the TNF-alfa induced IL-8 production at doses 10^{6-8} by the Caco-2 intestinal cell line, but on the contrary, at higher doses the level of IL-8 was increased by the same probiotic (Zhang et al., 2005). This finding indicates that the determination of the correct dose of a probiotic is of crucial importance for the appropriate treatment efficacy. The same study demonstrated also that heat-killed LGG was also able to decrease IL-8 production. This observation denied the paradigm that viability of probiotics is essential for their efficacy. Similarly, bacterial DNA from VSL#3, a high dose mixture of three strains of *Bifidobacteria*, four strains of *Lactobacilli*, and one strain of *Streptococcus salivarius* ssp. *thermophilus*, was able to decrease IL-8 secretion, delay NF-κB activation and stabilize IkappaB levels (Jijon et al., 2004). However, in another study using *Lactobacillus reuteri* on HT-29 and T84 cells only live but not deactivated bacteria reduced TNF-alfa induced IL-8 production and induced production of anti-inflammatory factors (Ma et al., 2004).
The most convincing evidence of the probiotic efficacy and mechanisms of action comes from animal studies. These experiments clearly demonstrated that the effect of probiotic

treatment depends both on the probiotic strain and the type of experimental inflammation. Not only live bacteria, but also soluble bacterial antigens extracted from different probiotic strains showed the ability to reduce the inflammation (Evaschuk et al., 2006). Therefore, viability of probiotic bacteria was not proven to be a prerequisite for their effect.

Author (year)	Probiotic	Treatment duration	N.(probiotic /control group)	Outcome N (probiotic/control group)
Kruis et al., 1997	*E. coli* Nissle 1917	12 wk	50/53	Maintenance of remission 42/51
Rembacken et al., 1999	*E. coli* Nissle 1917	12 mo	57/59	Induction of remission 39/44 Maintenance of remission 31/27
Ishikawa et al., 2003	Bifidobacteria-fermented milk (BFM)	12 mo	11/10	Maintenance of remission 8/1
Kruis et al., 2004	*E. coli* Nissle 1917	12 mo	162/165	Maintenance of remission 98/104
Cui et al., 2004	*Bifidobacteria* (3 strains)	8 wk	15/15	Maintenance of remission 12/1
Kato et al., 2004	*B. breve* strain Yakult, *B. bifidum* strain Yakult, *Lactobacillus Acidophilus*	12 wk	10/10	Induction of remission 4/3
Tursi et al., 2004	VSL#3	8 wk	30/30/30	Maintenance of remission 24/21/16
Furrie et al., 2005	*Bifidobacterium longum* +prebiotics	4 wk	9/9	Induction of remission 5/3
Sood et al., 2009	VSL#3	12 wk	77/70	Induction of remission 33/11
Miele et al., 2009	VSL#3	12 mo	14/15	Induction of remission 13/4 Maintenance of remission 11/4

Table 1. Randomized, controlled trials examining the effects of probiotics in inducing and/or maintaining remission in patients with ulcerative colitis

In the last years, many studies on the role of probiotics in UC have been published, however, many of them are small and methodologically weak. In the table 1 only randomized controlled clinical trials (RCT) addressing the role of probiotics in inducing and/or maintaining remission in patients with UC, published in the last years, are shown.

Rembacken et al. reported that probiotics (*E. coli* Nissle 1917) with steroids had similar efficacy compared to mesalazine with steroids in achieving remission, however, the relapse rate was slightly higher in the mesalazine group compared to probiotic group (73% vs. 67%, $P < 0.05$) (Rembacken et al., 1999). In 2004, Kato utilized a yogurt with *Bifidobacterium breve* strain Yakult, *B. bifidum* strain Yakult and a *L. acidophilus* strain, in addition to therapy with 5-ASA, in 20 patients with mild-to-moderate UC, and showed that this treatment was superior to conventional treatment alone in inducing remission as judged by clinical and endoscopic parameters (Kato et al., 2004). Tursi et al. used the probiotic mixture VSL#3 in 90 adults with mild-to-moderate active UC. In the probiotic group patients were treated with balsalazide and probiotic VSL#3. The first placebo group was treated with balsalazide alone and the second placebo group with mesalazine alone. Although they did not find the statistical significant difference in the proportion of patients of all three groups in achieving remission, the mean time to remission was significantly shorter in the probiotic group (4 vs 7 days, $P < 0.01$) (Tursi et al., 2004).

In a study by Kruis et al. there was no difference between the probiotic drug E coli Nissle 1917 and the standard therapy with mesalazine in maintaining remission in patients with ulcerative colitis (Kruis et al., 2004). In 2005, Furrie et al. reported results in 18 patients with active UC treated with a synbiotic preparation: a combination of a probiotic (*B. longum*) and a prebiotic (»Synergy 1«, an inulin-oligofructose polymer). The patients on the synbiotic appeared to have achieved clinical and endoscopic remission sooner, although the difference was only borderline significant ($p=0.06$) (Furrie et al., 2005). Miele et al. conducted the only published pediatric RCT on probiotics. In the study, children with a newly diagnosed mild or moderate UC were randomly assigned to receive either prednisone and mesalazine plus placebo, or prednisone and mesalazine plus VSL#3. At the end of induction therapy after 4 weeks, significantly more patients were in full remission if on VSL#3. In addition, colonoscopic and pathological scores assessed at 6 and 12 months were also significantly better in children on VSL#3. The percentage of patients without relapse at 1 year (80 vs 30%) was significantly better for the patients on the probiotic (Miele et al., 2009). A recent meta-analysis by Li-Xuan Sang et al. showed that using probiotics provided no additional benefit in inducing remission of ulcerative colitis. On the other hand, the probiotics auxiliary therapy was much better than non-probiotics therapy for maintenance treatment of UC (Li-Xuan et al., 2010). Based on the clinical trial evidence, available to date, *E. coli* Nissle and VSL#3 appear to be most effective in the management of UC. Therapy with *E. coli* Nissle 1917 for maintenance of remission of UC is now recommended in some European guidelines on the treatment of UC (Stange et al., 2008).

Pouchitis, chronic inflammation of ileal pouch created after proctocolectomy, may occur in approximately 30% of patients and is usually treated by antibiotics. However, in the last decade, the clinical efficacy of probiotic use in the maintaining of remission and the prevention of pouchitis was observed. Gionchetti et al. compared the efficacy of VSL#3 with placebo in maintenance of remission of pouchitis. The patients in the probiotic group relapsed in 15% when compared with 100% in the placebo group (Gionchetti et al., 2000). These results were replicated by Mimura et al. They found that the relapse rate after 12 months from the beginning of the therapy was 15% for VSL#3 group versus 94% for the placebo group (Mimura et al., 2004). In another study by Gionchetti et al. the efficacy of probiotic VSL#3 in the prevention of pouchitis after colectomy and pouch surgery was confirmed. During the first year after the operation, 10% of the patients on probiotic VSL#3 and 40% of the patients on placebo developed pouchitis (Gionchetti et al., 2003). In contrast

to probiotic VSL#3, the study with *Lactobacillus rhamnosus* GG observed alterations in intestinal microbiota but no other effects on clinical parameters (Kuisma et al., 2003). In a recent meta-analysis a search for randomized controlled trials (RCTs) of treatment and prevention of pouchitis from 1966 to October 2009 was performed. The primary objective was to determine the efficacy of medical therapies for pouchitis (including antibiotic, probiotic, and other agents) as substantiated by data from RCTs. For acute pouchitis, ciprofloxacin was more effective than metronidazole, while budesonide enemas and metronidazole were similarly effective. For chronic pouchitis, VSL#3 was more effective than placebo. For the prevention of pouchitis, VSL#3 was also more effective than placebo (Holubar et al., 2010). This meta-analysis confirmed the role of probiotic use for the treatment of chronic pouchitis and especially in prevention of pouchitis after ileal pouch-anal anastomosis.

7. Conclusion

The incidence of IBD in developed countries has increased over the last decades and is still increasing. The increase in the incidence cannot be explained only by the genetic background. Therefore, it is clear that the environmental factors play an important role. Several studies have been performed to clarify the role of nutritional factors in the development of UC and CD. There is some data showing that high intake of refined sugars, animal fat, red meat, omega-6 PUFAs and lower intake of omega-3 PUFAs may contribute to the increasing incidence of UC in the developed countries. Omega-3 PUFAs have been shown to have a beneficial effect in reducing gut mucosal inflammation, however, further studies have to be conducted to elucidate their exact role in the therapy of UC. Considering the important role of gut microbiota in the pathogenesis of UC, many efforts have already been made to change its composition in a way to decrease the inflammation and prevent exacerbations. With this intention, pre- and probiotics are being increasingly investigated. Clinical use of probiotics to date has been proved effective in the therapy of pouchitis and maintenance of remission in ulcerative colitis.

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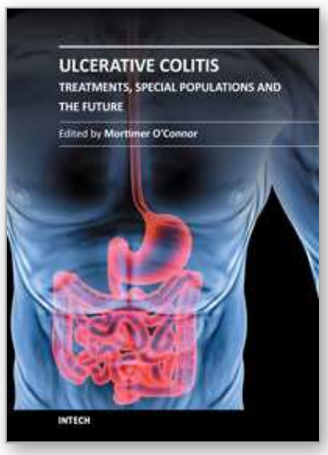

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