FOOD, NUTRIENTS AND NUTRACEUTICALS AFFECTING THE COURSE OF INFLAMMATORY BOWEL DISEASE

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ABSTRACT

Inflammatory bowel diseases (ulcerative colitis; Crohn's disease) are debilitating relapsing inflammatory disorders affecting the gastrointestinal tract, with deleterious effect on quality of life, and increasing incidence and prevalence. Mucosal inflammation, due to altered microbiota, increased intestinal permeability and immune system dysfunction underlies the symptoms and may be caused in susceptible individuals by different factors (or a combination of them), including dietary habits and components. In this review we describe the influence of the Western diet, obesity, and different nutraceuticals/functional foods (bioactive peptides, phytochemicals, omega 3-polyunsaturated fatty acids, vitamin D, probiotics and prebiotics) on the course of IBD, and provide some hints that could be useful for nutritional guidance. Hopefully, research will soon offer enough reliable data to slow down the spread of the disease and to make diet a cornerstone in IBD therapy.

KEYWORDS

Inflammatory bowel disease, ulcerative colitis, Crohn's disease, nutraceuticals, functional foods

Introduction

Inflammatory bowel diseases (IBD) are chronic relapsing inflammatory disorders of the gastrointestinal tract whose incidence and prevalence is alarmingly increasing. The two main kinds of IBD are ulcerative colitis (UC) and Crohn's disease (CD). Although differentiated by their location and behavior (Table 1), both are debilitating conditions, which also carry an increased risk of colorectal cancer (CRC) [1].

Different etiological factors may be involved in IBD development, including environmental factors, infectious diseases, ethnicity, genetic susceptibility and dietary habits. An individual's susceptibility to IBD probably depends on the interaction of all these factors [1,2]. All of them may cause intestinal microbiota modifications, increased intestinal permeability, increased uptake of harmful adjuvants and antigens, and immune system dysregulation through different mechanisms (Table 2), leading to an altered balance between pro-oxidant and anti-oxidant mediators, pro-inflammatory and anti-inflammatory environment, Th1- and Th2-mediated responses. The final result is mucosal inflammation, which is considered to be the main cause of discomfort in IBD patients [3-8]. Approved drugs for IBD treatment and other therapeutic approaches are summarized in Table 3.

IBD is more prevalent in the Northern than the Southern part of the world, particularly among Caucasian populations. The incidence of IBD is highest in westernized nations, with the highest reported incidence rates in North America, Northern Europe, the United Kingdom and Australia (Table 4) [9,10,11]. However, the rapid increase in IBD incidence and prevalence in recent decades, particularly in countries with previously lower morbidity rates, such as

those in South-Eastern Europe, Asia and much of the developing world, strongly suggests an environmental trigger for these diseases, including westernization of lifestyle, and changes in diet [10].

Dietary components, such as omega-6 polyunsaturated fatty acids (ω6-PUFAs), long-chain saturated fatty acids, protein, and digestible carbohydrates, may contribute to IBD pathogenesis through altering intestinal microbiota, increasing intestinal permeability, and promoting inflammation. In contrast, omega-3 polyunsaturated fatty acids (ω3-PUFAs), medium chain triglycerides, bioactive food-derived peptides, and non-digestible carbohydrates seem to improve these parameters and intestinal health [5]. Other dietary components, particularly those with anti-oxidant and anti-inflammatory properties, as well as probiotics and prebiotics, with potent effects on gut microbiota, may be beneficial to improve symptoms and reduce relapses in IBD patients, and are currently the focus of intense research.

Thus, dietary habits and constituents may trigger or protect, as well as reduce or increase activity of the inflammatory process in IBD, altering symptoms and quality of life. In this review, we will describe the role of the main dietetic factors thought nowadays to influence the course of IBD (Western diet and obesity, and nutraceuticals), and will provide some hints on dietetic management of IBD, both during active and remission phases.

Relationship of IBD with Western diet and obesity

The Western diet, also called Western dietary pattern or the “meat-sweet” diet, is characterized by higher intakes of red and processed meat, butter, high-fat dairy products, eggs, refined grains, white potatoes and French fries in particular, and high-sugar drinks [12]. It is in high contrast with non-Western diets, like the Mediterranean diet, which has higher levels of fruits, vegetables, whole-grain foods, poultry and fish [13]. The Western diet has been implicated in many diseases and different epidemiological data suggest that consumption of a Western diet is associated with increased IBD risk (Table 5) [1,9].

Retrospective studies identified an increased consumption of monosaccharides prior to IBD occurrence [14,15]. Different studies have shown a negative effect of sweets and artificial sweeteners on the risk of developing both UC and CD [16,17]. However, a prospective study with 400,000 participants demonstrated no association between total intake of carbohydrates, sugar or starch on incidence of UC or CD [18]. Very recently, the European Prospective Investigation into Cancer (EPIC) study, including more than 350,000 European participants with IBD, has shown no association between dietary pattern and either UC or CD risks, but an imbalanced diet, with high consumption of sugar and soft drinks and low consumption of vegetables, was associated with UC risk [19].

Although an increased consumption of animal protein may slightly increase the risk of IBD development [15], animal protein-derived bioactive peptides might be beneficial, as discussed below.

More evidence has been accumulated towards the negative influence of a diet high in fat, particularly cholesterol and animal fats, trans fatty acids, and linoleic acid, an ω6-PUFA precursor of arachidonic acid, whose metabolites (PGs, LTs) exhibit pro-inflammatory properties [15,20,21]. Many naturally occurring agents, including arachidonic acid and its metabolites, bind with and activate peroxisome proliferator-activated receptor γ (PPAR-γ), a type II nuclear receptor that regulates fatty acid storage and glucose metabolism. The genes activated by PPAR-γ stimulate lipid uptake by adipocytes and play an important role in regulating inflammation and cancer cell growth [22]. It has been suggested that PPAR-γ targeting, by either drugs or nutrients, could prevent colonic inflammation by restoring antimicrobial immunity in CD [23]. Conjugated linoleic acid modulates immune responses in patients with mild to moderately active CD [24], maybe through modulation of PPAR-γ. A high intake of total, trans, saturated and monounsaturated fats and a higher ratio of ω6/ω3 PUFAs were associated with a more active phenotype of CD; this was particularly detrimental to individuals carrying certain single nucleotide polymorphisms (SNPs) [25].

In contrast, oleic acid, a monounsaturated fatty acid present in olive oil [26], and different dietary ω3-PUFAs exert protective effects, as discussed further in this review.

A low-fiber diet may increase the risk of CD, and, if associated with high consumption of sugar and soft drinks, it may also increase UC risk [19]. In contrast, high-fiber diets (not typical of a Western diet), particularly those in which fiber originates from fruit sources, decreased the risk of developing CD [17,27]. Moreover, the anti-inflammatory and anti-oxidant activity of vitamins

and minerals (vitamin C, magnesium) contained in fruits and fruit juices are protective, and citrus fruits are particularly recommended [16]. Soluble and insoluble dietary fiber are essential for gastrointestinal mucosa health, and their relationship with IBD will be described in depth below (see Probiotics and prebiotics).

The Western diet is characteristically associated to the development of obesity, which has been linked with excess adipocyte hypertrophy, generating a pro-inflammatory state through secretion of inflammatory cytokines and chemokines [28-30]. These biofactors might be closely related to IBD pathogenesis. However, body mass index (BMI) was not associated with IBD morbidity (neither CD nor UC) [31], suggesting that increased caloric intake and increased BMI *per se* might not be enough to trigger IBD development [32].

Interestingly, more specific factors related to adipose tissue may be more influential in the development of IBD, particularly CD [33], such as fat wrapping or “creeping fat”, the fat extending from the mesenteric attachment to partially cover the small or large intestine [34]. This fat is positively correlated with muscular hypertrophy, fibrosis, transmural inflammation, and stricture formation at the gross level, and macrophage and lymphocyte perivascular infiltration on histology [35]. Thus, it has been suggested that fat accumulation in the mesentery of patients with CD could be related to IBD pathogenesis, with participation of cytokines (TNF-α, C-reactive protein), adipokines (leptin, adiponectin, resistin), and neuropeptides (substance P, neurotensin) [33]. However, it has been suggested that “creeping fat” might actually play a protective role during CD, with increased production of anti-inflammatory

cytokines compared to those isolated from distal sites which have a cytokine profile similar to adipocytes isolated from obese patients [36]. Interestingly, adipose tissue-derived stem cells decreased inflammatory responses in dextran sodium sulfate (DSS) colitis mouse model, including the down regulation of pro-inflammatory cytokine expression from macrophages [37].

Subtle differences are present in adipose tissue from obese and IBD patients [33]: origin of the mesenteric fat (hyperplastic in IBD, *vs*. hypertrophic in obesity); adiponectin levels (increased in IBD *vs*. decreased in obesity); origin of TNF-α (from adipocytes in IBD *vs*. stromal vascular cells in obesity). Although in both conditions adipokines are dysregulated as part of a chronic inflammatory condition, obese individuals rarely develop symptoms of IBD, and metabolic syndrome is rare in IBD patients (unless related to chronic corticosteroid use).

How these differences account for the disparity of symptomatology between obesity and IBD is not at all clear at this stage [33]. Despite the fact that both conditions might be related to the Western diet, their differences in fat deposition and regulation suggest that distinct key factors (genetic, environmental or both) may be involved, leading to one or the other. These are still to be identified.

In the following sections, we will describe the role of particular dietary components with specific health-promoting functions in IBD. Due to these properties, they are considered nutraceuticals or functional foods. As such, they may prevent the onset of the disease or improve its symptoms, which makes them interesting coadjutants in drug treatment.

Bioactive dietary peptides and amino acids

In addition to their nutritional properties, an increasing number of amino acids (AAs) and peptides are recognized to exert beneficial effects in health [6,38]. Bioactive AAs and peptides are generated from food proteins through gastrointestinal digestion, chemical and enzymatic hydrolysis, or bacterial metabolism.

Egg yolk, soy and milk-derived peptides reduce oxidative stress in the gut. This antioxidant activity may be beneficial in IBD since increased oxidative stress with decreased antioxidant defenses were identified in colonic mucosal biopsies of patients [39]. The antioxidant efficacy of these functional peptides is determined by AAs at C-terminal regions [40]. Isolated AAs may also reduce oxidative stress in the gut, particularly those containing a thiol group (cysteine, methionine, taurine) or an aromatic side chain (tryptophan, tyrosine, phenylalanine). Their antioxidant properties have been demonstrated using *in vitro* and *in vivo* models of IBD (see [6] for review). Glucosinolates and S-methyl cysteine sulfoxide contained in cruciferous vegetables, such as cabbage and broccoli, seem to be particularly beneficial in some CD patients [41].

Different peptides from soy or whey protein showed anti-inflammatory effects in colonic tissue, mainly due to a reduction in pro-inflammatory cytokine release. Dietary alanine-glutamine dipeptide reduced expression of inflammatory mediators and elevated expression of mucin 2 and heat shock protein 72, enhancing recovery of mucosa in the DSS-induced UC mouse model [42]. The dipeptide flavor enhancers γ-glutamyl-cysteine and γ-glutamyl-valine were capable of inhibiting inflammation in both *in vitro* and *in vivo* IBD models [6,43].

In another study, bovine milk protein κ-casein-derived glycomacropeptide exerted intestinal anti-inflammatory effects in a lymphocyte-transfer mouse model of colitis [44]. It reduced the activity of colonic myeloperoxidase and reduced the percentage of $CD4^+$ IFN-γ^+ cells in mesenteric lymph nodes. Bowman-Birk inhibitors, a type of small bioactive sulfur peptides from legume seeds (peas, beans, soy…), are able to diminish inflammation markers and tissue damage in colitis mice models [45].

Some AAs may also have anti-inflammatory and anti-apoptotic effects in the gut system. A decrease in tryptophan has been found in human IBD patients [46], and tryptophan showed beneficial effects in a DSS-induced porcine IBD model [47]. Tryptophan reduced inflammation by inhibiting the Th1-mediated response, amongst other effects, through T cell apoptosis induction.

Glutamine is known to repair the epithelial layers, maintain intestinal mucosa function, and enhance the immune responsiveness [48]. In experimental colitis, glutamine inhibited inflammatory responses by regulating NF-κB activation [49]. In addition, it increased autophagy activity and autophagosome formation, which are essential to eliminate and recycle damaged/unwanted proteins and organelles, as well as to remove intracellular pathogens, to facilitate innate immunity and to modulate cell death [6].

An increase in dietary cysteine enhanced mucin synthesis in a DSS-treated rat model [50]. Mucins are cysteine-rich glycoproteins very important for intestinal epithelial integrity. They are secreted by goblet cells and protect the intestinal epithelium from damage caused by digestive fluid, microorganisms and toxins. Supplementation with L-cysteine in a porcine model of DSS-induced colitis

reduced local chemokine and pro-inflammatory cytokine expression and neutrophil influx, thereby attenuating the intestinal inflammatory responses and restoring immune homoeostasis [51].

Dietary AAs and peptides may exert their beneficial action through regulation of cellular signal transduction and gene expression, after interacting with cellular membrane receptors or after being transported into cells. These novel mechanisms of action have only recently been investigated. Di- or tripeptides may be transported across the brush border into enterocytes (where they are converted into either AAs or released), or may pass through intestinal epithelial cells and enter the portal circulation via hPepT1 (intestinal proton-dependent peptide transporter) delivery [52]. This transporter might be an alternative mechanism by which short-chain dietary peptides exert their anti-inflammatory activity to attenuate the inflammatory responses in colonic epithelial cells, as has been demonstrated for the meat-derived dipeptide carnosine and the soy protein-derived tripeptide valine-proline-tyrosine, in both *in vitro* and *in vivo* assays [53,54].

Another mechanism of AAs and peptide anti-inflammatory activity involves the activation of the calcium-sensing receptor (CaSR), a seven transmembrane-spanning G protein-coupled receptor capable of sensing changes in extracellular calcium concentration, and involved in different cellular activities (secretion, apoptosis, proliferation, differentiation and ion-channel activity). Diet-derived CaSR agonists present in the colon, such as polyamines, may activate this receptor [55]. Activation may lead to regeneration of the intestinal barrier [56]. Increased dietary calcium intake leads to prevention of CRC development and promotes colonic mucosal epithelial cell differentiation in a CaSR-

dependent fashion [57,58], contributing to gut homeostasis. Also allosteric modifiers (γ-glutamyl dipeptides, aromatic AAs) may modulate the activity of CaSR, leading to potent anti-inflammatory effects via attenuation of TNF-α signaling events. Thus, CaSR expressed along the GI tract may be a novel therapeutic target for dietary peptides or AAs capable of enhancing gut health.

Dietary lipids and fat-soluble vitamins

Epidemiologic observations revealed a low incidence of IBD in eskimos, whose diet is rich in oily fish. This has led to intense research trying to assess the preventive and therapeutic potential of ω3-PUFAs. The most important ω3-PUFAs in human diet are DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid), which have been tested for prevention of different inflammatory diseases in animals and humans, including IBD [3].

ω3-PUFAs (from fish oils and some seed oils) are potent anti-inflammatory nutraceuticals, capable of inhibiting the biosynthesis of important inflammation elicitors such as PGE_2 and TNF-α. In addition, ω3-PUFAs also act as substrates for the synthesis of the inflammation resolving mediators resolvins, maresins and protectins. Other mechanisms of their anti-inflammatory action include decreasing the expression of adhesion molecules, inhibition of the pro-inflammatory transcription factor NF-κB, activation of the anti-inflammatory transcription factor PPAR-γ, and binding to the G protein coupled receptor GPR120 [3,59]. Many of these mechanisms are interlinked and, although the

full extent of this is not yet elucidated, they are seen as potentially useful for IBD treatment.

Production of PGE_2 and TNF-α pro-inflammatory cytokines (and others like IL-1β) is dependent on NF-κB activation at IBD mucosa cells. NF-κB is a pro-inflammatory transcription factor produced under altered epithelial permeability barrier conditions, including IBD [60]. Thus, ω3-PUFAs can inhibit IL-1β and TNF-α production [61], and act as free radical scavengers [62,63].

In the case of PGE_2, its biosynthesis is inhibited by ω3-PUFAs as they avoid the conversion of arachidonic acid (an ω6-PUFA) towards pro-inflammatory PGs and LTs. EPA and DHA can replace arachidonic acid and inhibit pro-inflammatory mediators production, including that of LTB_4 and thromboxanes (TX), which are elevated in the inflamed intestinal mucosa [62]. TXA_2 may be especially important since it modulates platelet aggregation, and gastrointestinal infarctions have been suggested as one of the first pathogenic steps in CD [64]. Accordingly, treatment with ω3-PUFAs decreases platelet responsiveness in patients with IBD [65].

Experimental models of colitis have been used to study the effects of dietary ω3-PUFAs. These studies report that marine ω3-PUFAs decrease chemically-induced colonic damage and inflammation compared with an ω6-PUFA-rich diet [59,66]. These effects were associated with a reduction in the amount of LTs, TXB_2 and PGs. Similarly, transgenic mice rich in endogenous ω3-PUFA (fat-1 mice) showed much less colonic damage and inflammation, with less TNF-α, IL-1β and NF-κB activation, and more resolvins, among other protective

mediators, compared to wild type mice [67]. Resolvins have shown their ability to protect against chemically-induced colitis [68].

Based on these evidences, many authors have studied the role of ω3-PUFAs in prevention and treatment of inflammation in IBD in humans. However, these reports show conflicting results. In some of them, ω3-PUFAs had an important role in the course of CD and UC, with reduced inflammation, improved clinical benefits and lower rates of relapse. However, others provided inconclusive or negative results [3,59,69]. Moreover, meta-analyses considering maintenance of remission in patients with CD or UC identified little effects [70,71].

The controversial findings on the relationship between the anti-inflammatory properties of ω3-PUFAs and the results of trials with IBD patients may be due to differences in study design (number of patients, period of study, heterogeneity of population lifestyle, etc), amount and formulations of the fatty acids administered, or patient compliance. These aspects may interfere with the efficacy of ω3-PUFAs. Thus, although animal experiments demonstrate the benefits of ω3-PUFAs, clinical trials show only weak evidence of their benefit in human IBD. Intriguingly, 2 g per day seem to be enough to achieve an anti-inflammatory therapeutic efficacy in rheumatoid arthritis. Therefore, more studies are needed to elucidate the pathophysiological mechanisms and establish a consensus on ω3-PUFAs dietary recommendations for IBD patients [3,5,59].

It is also of interest to discuss the roles of fat-soluble vitamins, particularly that of vitamin D. Fat-soluble vitamins such as A, D, E, K are significantly decreased in patients with CD. Furthermore, animal models suggest that vitamin D plays

an important role in the pathogenesis of IBD, and in mice models for UC, vitamin D supplementation ameliorates symptoms [72].

Vitamin D serum levels are associated to protection against CRC and IBD, as this compound shows potent anti-inflammatory activity [73]. Interestingly, IBD and CRC are more frequent in Northern latitudes, where populations are also more defective in serum vitamin D due to sunlight deficiency during winter [74]. In fact, in the Northern hemisphere, the onset of UC and CD are noted to peak in winter. Other factors involved could be the variability of receptor polymorphisms, an inadequate dietary intake, impaired conversion of vitamin D to its active metabolite (1,25(OH)2D), or its increased catabolism and excretion [75-77].

The role of vitamin D in IBD seems to be multifactorial, comprising both maintenance of musculoskeletal health and immunomodulation of disease activity. Thus, patients with IBD are at increased risk of diseases related to calcium homeostasis like osteoporosis [78,79]. In fact, the prevalence of low bone mineral density is greater in patients with IBD than in healthy controls with up to 41% suffering osteoporosis [80]. Similarly, a chronic inflammatory state, with effects on osteoblast and osteoclast function mediated by cytokines such as TNF-α, IL-6 and IL-1β, contributes to bone loss [81]. On the other hand, evidences of the role of vitamin D in immunomodulation of IBD are broad [78], since it inhibits pro-inflammatory cytokine production (TNF-α, IFN-γ, IL-21 and IL-6) [82]. Vitamin D has also been shown to stabilize the epithelial barrier, by means of claudin-2 inhibition in UC and increased tight junction proteins (occludin, zonulin-1…) expression *in vitro* [78,83]. In addition, it promotes

intracellular bacterial degradation by macrophages via cathelicidin in UC [84] and autophagy via NOD2 in UC and CD [85]. NOD2 has also been associated with distinct roles in mucosal immunity such as negative regulation of toll-like receptor (TLR) signaling and promotion of IL-10 secretion [86].

Serum 25-hydroxyvitamin D (25(OH) D) is the common way to measure patients' vitamin D status. There is strong evidence to support a high prevalence of significantly lower serum 25(OH) D levels among the IBD population, which have been shown to correlate with increased disease activity [76,87,88]. In epidemiological studies, serum levels below 30 nM of 25(OH) D have even been associated with higher incidence of CRC [89]. However, some data are conflicting. A retrospective study [79] concluded that vitamin D deficiency was associated with lower health-related quality of life and increased disease activity in patients with CD but not with UC. Ananthakrishnan et al [90] examined the association between vitamin D deficiency and the need for IBD-related surgery, measuring plasma 25(OH) D levels. They found that plasma 25(OH) D < 20 ng/mL was associated with an increased risk of surgery and hospitalization compared with those with sufficiently high levels. Only CD patients who normalized their plasma 25(OH) D had a reduced likelihood of IBD-related surgery compared with those who remained deficient. A significantly lower C-reactive protein was also seen in these patients. Similarly, the measurement of plasma 25(OH) D levels in an anti-TNF therapy protocol with CD and UC patients demonstrated a significant inverse association with durability of anti-TNF treatment, with a more pronounced effect on patients with CD [91]. To date, only two small open label trials and one randomized

controlled trial have shown a positive effect of vitamin D supplementation on disease activity in patients with CD; no effect has been shown for UC [92].

An optimal vitamin D supplementation protocol for patients with IBD remains undetermined since it depends on factors like the basal vitamin D concentration, among others [76,78,88]. Similarly, it is necessary to consider the toxicity, although rare, that may result from an excess of 25(OH) D levels [78].

In summary, studies suggest that ω3-PUFAs may lead to the production of anti-inflammatory factors possibly benefiting IBD patients. Unfortunately, there is currently no clear evidence of their efficacy. Similarly, increasing preclinical and clinical evidence suggests a role for vitamin D deficiency in the development and severity of IBD but its efficacy is far from clear, particularly in UC patients. Further research is required to determine optimal ω3-PUFAs and vitamin D levels, which will achieve beneficial effects, and to support their role in inducing disease remission and preventing relapses or long-term complications.

Phytochemicals

There are many plant-derived nutraceuticals or phytochemicals with healthy properties. Anthocyanidins are potent anti-inflammatory and anti-oxidant flavonoids present in some herbal flowers (hibiscus), fruits (blueberries, raspberries) and red wine. UC patients receiving an anthocyanidin extract daily for 9 weeks at the time of symptoms onset showed 63% remission [93].

Acute colitis in an animal model has also been partially inhibited by two other flavonoids, eupatilin and quercetin, orally administered 48 h prior to colitis agent challenge. Rats receiving the flavonoids extracts showed less mucosa lesions, nitric oxide production (involving a protective role at the mucosa as less oxidative damage takes place) and TNF-α, but higher glutathione levels [94].

In a similar way, UC patients receiving 1 g/day of curcumin (another pigmented plant polyphenol nutraceutical with inhibitory effects against TNF-α, NF-κB and TLR-4) *plus* mesalamine showed lower recurrence rates than the placebo *plus* mesalamine cohort [95]. Interestingly, in animal models of UC, curcumin pre-treatment (at 100 mg/kg body weight) before DSS challenge partially protected the mice against colitis symptoms [96].

Other phytochemicals with potentially beneficial effects in IBD due to their antioxidant, anti-inflammatory and gut microbiome protective properties are epigallocatechin gallate (present in green tea [97]), ellagic acid and ellagitannis (found in some fruits and nuts like boysenberries, chestnuts and pomegranates [98]) and resveratrol (from red wine), which might also have a protective role in gut inflammation and progression to CRC [99].

Probiotics and prebiotics

Probiotics have been defined by FAO/WHO as “live microorganisms that confer a health benefit to the host when administered in adequate amounts”. Especially in combination with prebiotics (plant substrates that enable modulation of colonic microbiota), these may be especially beneficial to CD

patients [100,101]. Probiotics are believed to be capable of modifying the flora in the intestine, replacing the harmful microbes by useful ones.

Early studies showed a dysbiosis in IBD patients' microbiota, with lower levels of beneficial bacteria like *Bifidobacteria*, and higher numbers of potentially harmful taxons as *Proteobacteria* [102,103]. Based on these studies, diverse clinical trials have been made in these patients with probiotic species including *E. coli* Nissle 1917*, Lactobacillus casei, L. rhamnosus* GG, *Bifidobacterium spp.* and *Saccharomyces boulardii.*

Thus, *E. coli* Nissle 1917 at 10^{10} CFU/day was able to maintain the remission status in 70% of CD patients for over a year when administered together with prednisolone, in comparison to 30% remission maintenance in placebo *plus* prednisolone cohort [104].

L. rhamnosus GG diminished about 73% of CD relapses when administered at 10^{10} CFU/day together with prednisone, along a 6 month trial. This prevention effect disappeared a few weeks after probiotic suspension [105]. This bacterium also shows a beneficial stimulus on enterocytes proliferation, by activation of Erk1/2 cell cycle MAPK, therefore contributing to diminish mucosal damage and epithelium atrophy in these patients [106]. Other related bacteria, such as *L. bulgaricus* OLL1181, are able to protect mice against DSS-induced colitis through activation of the aryl hydrocarbon receptor (AhR), a novel mechanism of protection against IBD [107].

Administration of *S. boulardii* yeast, together with the drug mesalamine (2 g/day), has been able to reduce clinical relapses of CD to 6.25% versus 37.5% relapses in the control group (only mesalamine treatment) over a 6 month

period [108]. However, administration of just the probiotic yeast, did not show a positive effect in another study with this type of patients [109].

The commercial fermented milk Yakult (*B. breve, B. bifidum* and *L. acidophilus*) was able to get 73% remission in UC patients after one-year consumption (10^{10} CFU/day) in comparison to 10% remission for placebo cohort [110]. *B. infantis*, administered together with the prebiotic inulin, was able to diminish production of pro-inflammatory cytokines like IL-8 in a DSS rat model for UC, enhancing also the epithelium barrier function [111].

Diverse mechanisms of action have been proposed to explain how these probiotics are able to modulate IBD symptoms. These include, on the one hand, colonization of the colon (by probiotics binding to specific enterocytes receptors) and inhibition of pathogens growth (by production of bacteriocins, lactic acid, acetic acid or H_2O_2) [112-115]. On the other hand, probiotics show interaction with epithelial and immune cells in the intestinal mucosa, enhancing the barrier function. This can be achieved by increasing mucus production [116] or by enhancing tight junctions by means of overexpression of occludin and zonulin-1 [117,118] and the immune response (e.g. by increasing IgA production, natural killer cells activity and phagocytosis) [119-121]. For example, the polysaccharide A from *Bacteroides fragilis* is able to induce regulatory T cell proliferation, which shows anti-inflammatory potential, diminishing UC symptoms in a mouse model after infection with the pathogen *Helicobacter hepaticus* [122]. Colonization of germ-free mice by *E. coli* triggers production of IgA [123]. The probiotic *Propionibacterium freudenreichii* is able to reduce the levels of pro-inflammatory cytokines produced by gut mucosa macrophages, therefore attenuating IBD and mucosa inflammation in a mice model. The

bacterial molecule responsible for this protective inhibition is DHNA (1,4-dihydroxy-2-naphtoic acid), a prebiotic compound, which also promotes *Bifidobacterium* growth [124].

These bacteria-enterocytes interactions use diverse messengers as extracellular enzymes (e.g. the transaldolase for binding of *B. bifidum* to enterocytes), bacterial peptides, lipopolysaccharide and peptidoglycan subunits [125-127].

Currently, the role of 50-250 nm outer membrane vesicles (OMVs, from Gram negative gut microbiota) has been highlighted for transportation of miRNA, DNA and peptides (virulence factors, immunomodulators) through the mucin layer towards the enterocytes monolayer and beyond (liver, brain and other tissues), where their contents exert important regulatory impacts [128]. For example, the pathogen *Campylobacter jejuni* secretes OMVs with cytotoxic activity on enterocytes, triggering IL-8 production and causing proteolysis of tight junctions, contributing to gastroenteritis onset [129]. Similarly, the probiotic *Akkermansia muciniphila* generates membrane vesicles that inhibited secretion of the pro-inflammatory IL-6 even in the presence of *E. coli* OMVs, and also showed protection against DSS-induced UC in mice [130].

Another positive effect of probiotics on intestinal mucosa health is derived from their ability to induce activation of NADPH oxidase-1 (Nox1), an important generator of ROS in charge of defense mechanisms against pathogens invasion at mucosa level [131].

Although all these examples show how diverse and beneficial the bioactivities of different probiotics are with respect to protection from IBD, in most cases,

administration of these probiotics to patients is not going to produce a long lasting effect, unless prolonged gut colonization by these probiotics is achieved. For example, adults show lower counts of *Bifidobacterium* in their gut, in comparison with infants receiving breast milk. This and other prebiotic species contribute to maintenance of gut homeostasis by: (1) nutritional competition with pathogenic and other commensal bacteria; (2) competitive exclusion of adhesion places at gut mucosa, generating a cell barrier function; (3) immune system stimulation via dendritic cells (via interaction with TLRs and Nod-like receptors, NODLR); (4) generating short-chain fatty acids, SCFAs, from prebiotics fermentation; (5) inhibiting inflammation-associated pathways (such as those dependent on NF-kB); (6) producing vitamins; and (7) producing diverse bacteriocins and other substances able to carry out a direct antagonism function in non-beneficial bacterial species [132].

Importantly, IBD patients show lower bacterial diversity in gut microbiota, with higher numbers of *Enterobacteriaceae,* fungi and methanogens, and lower *Bacteroidetes* populations [133,134]. Also, this gut microbial dysbiosis has been recently associated to changes in the electrolyte homeostasis in the gut lumen, since disruption of Na^+/H^+ exchangers (as NHE3) in a mice model causes gut microbial dysbiosis (reduced *Lactobacillaceae*, *Ruminococcaceae*, and increased *Erysipelothrichaceae*) and IBD symptoms (increased IL-1β, TNF and IFN-γ levels) [135]. The presence of certain pathogenic and commensal bacteria in these overrepresented groups, as well as diverse bacterial antigens in the gut ecosystem, has been associated to IBD in some cases. For example, *NOD2* codes for an intracellular receptor for peptidoglycan, and some polymorphisms in this gene have been associated with IBD in 30% of patients

in Europe [136]. NOD2 activation by peptidoglycan triggers NF-kB transcriptional factor, and mitogen-activated protein kinase (MAPK) pathways, generating pro-inflammatory cytokines like IL-1β and TNF [137].

Enhancement of targeted probiotic numbers can be obtained by supplying the gut ecosystem with a specific type of non-digestible oligo- or polysaccharides that selectively stimulate these beneficial bacteria, therefore improving host health. These saccharides are called prebiotics [138].

Two probiotic genera which result favored by the ingestion of prebiotics are the already mentioned *Lactobacillus* and *Bifidobacterium*, which, together with other beneficial gut species, will finally contribute to prebiotics fermentation towards SCFAs like acetate, propionate and butyrate. SCFAs are important protective factors against CRC, as they possess apoptotic induction activity on tumor cells through inhibition of histone deacetylases. SCFAs, and in particular butyrate, are important energy fatty acids for normal colonocytes, contributing to their homeostasis [139].

Diverse prebiotic fiber, like the lactulose disaccharide, inulin and fructooligosaccharides (FOS) or goat's milk oligosaccharides are able to reduce inflammation parameters in IBD patients (15 g/day) and animal models (5 g/kg body weight), lowering the levels of pro-inflammatory cytokines (such as IL-1β, IL-17, TNF-α), and at the same time increasing the levels of their anti-inflammatory counterparts (such as TGF-β) [140-143].

Prebiotics are able to restore the mucus barrier integrity, preventing bacteria and some of their metabolites from reaching the epithelium. This barrier is also destroyed in DSS-induced animal models for UC, and under this pathological

situation, lumen bacteria reach the enterocytes [144-146]. SCFAs produced from prebiotics fermentation, like butyrate, when administered orally to IBD animal models, protect against mucus layer destruction, as this SCFA promotes MUC2 and mucin glycoltransferases expression [147].

In spite of these data, some authors do not find enough evidence to recommend dietary supplementation with prebiotics in CD or UC [148].

Dietetic management of inflammatory bowel diseases

Despite intense research to determine the role of dietary factors in IBD, as shown above, in clinical practice this role seems to be underestimated, except for exacerbations. In fact, clinical remission and mucosal healing can be achieved in active CD by a switch from normal diet to a formula–defined enteral feed. Different mechanisms for this response may be involved: changes in nature or quantity of gut bacteria, improved nutritional status, reduced allergenicity of gut contents, avoidance of food additives or provision of an anti-inflammatory factor such as TGF-β [149-150]. Evidence for an impact of diet on UC is much weaker and, so far, for neither disease is there convincing evidence from interventional studies to implicate any specific foodstuffs.

Importantly, approximately 70% of IBD patients employ elimination diets while in remission, affecting their social and family life [1]. These are generally self-imposed diets, frequently based on non-medical resources (such as patient support groups and unverified sources on the internet), with highly questionable results [151], and not supported by the different gastroenterology organizations

[152-155], which generally recommend, instead, a “well balanced diet”, supplying an appropriate amount of energy, iron, calcium, zinc, folic acid and vitamins D and B_{12} [155]. Thus, non-hospitalized IBD patients are not currently being given nutritional guidelines outside those for the general population. However, it has been claimed that nutrition, based on genetic and epigenetic individual characteristics [156], should become a primary therapy for IBD in its own right, with significant benefits in terms of delaying IBD progression, decreasing sanitary costs, and reducing the possibility of CRC formation.

Table 6 shows a recent dietary guide for IBD patients based on the best available evidence from experimental, epidemiological and interventional studies [148]. Other recent reviews on dietary recommendations for IBD patients can be seen in [1,151,157]. Here two particular kinds of elimination (gluten-free and FODMAP) diets will be addressed.

Dietary antigens may alter the gut microbiome, and affect gastrointestinal permeability. Patients with IBD are known to have increased antibodies to several food and bacterial antigens [158]. Thus, eliminating the food component responsible for the associated immune reactions is often enough to avoid relapse. Gluten may be one of these components.

Gluten-related disorders include 3 main forms of disease: celiac disease (an autoimmune disease), wheat allergy (an IgE mediated response), and non-celiac gluten sensitivity (NCGS) [159]. The prevalence of IBD in celiac patients has been reported as being 5-10 times higher than in the general population [160]. In addition, in IBD patients showing NCGS, gluten may cause intestinal (diarrhea, bloating, abdominal pain) and extraintestinal (fatigue, nausea)

symptoms (similar to those found in irritable bowel syndrome, IBS), and these patients report symptom improvement and fewer flare-ups of IBD on a gluten-free diet [161]. However, it has been suggested that other non-gluten components of grain (fermentable carbohydrates, amylase trypsin inhibitors and wheat-germ agglutinin) might also be responsible for NCGS [162]. Intense research is currently focused on this issue.

FODMAP is an acronym of “Fermentable Oligo-, Di-, Mono and Polyols”. A low FODMAP diet (i.e., low in wheat, onions, beans, many kinds of fruit and sorbitol) appears to reduce some of the symptoms in CD and other functional gastrointestinal disorders, especially IBS [163,164]. Since most patients with small intestinal CD are likely to develop strictures at some time in the course of their disease, it seems appropriate to recommend a low intake of foods that are high in insoluble fiber [1,148]. However, against this FODMAP diet, there is a concern that such a structured dietary regime will have adverse effects in reducing dietary diversity. It is particularly important to recognize that this very same group of excluded nutrients plays a major role in modulating the composition of gut microbiome (most/all prebiotics are FODMAPSs) [148,165]. Thus, a low FODMAP diet may be worth trying in patients with IBD who have “IBS-type” symptoms such as bloating or watery diarrhea that have persisted despite appropriate treatments for underlying active IBD or bile salt malabsorption [148]. Nevertheless, care needs to be taken that patients following this diet do not restrict their fruit and vegetable intakes too severely, in order to avoid vitamin and mineral deficiencies.

Conclusions

The main dietary factors that may influence the course of IBD have been reviewed. Whereas the imbalanced Western diet may trigger the disease in susceptible individuals, several nutraceuticals and functional foods (bioactive peptides, ω3-PUFAs, vitamin D, phytochemicals, probiotics and prebiotics) are proposed to prevent the disease or to aid in its treatment. However, there is still not enough convincing evidence to support firm nutritional guidelines, and patients often try to empirically adjust their diet or seek help from non-reliable sources. Since IBD incidence and prevalence is increasing at alarming rates, more basic research and clinical trials are urgently needed to better define the effects of dietary factors (alone or in combination), and the administration pattern that would optimize the efficacy and safety profile, and hopefully prevent the development of IBD.

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Table 1. Key differences between ulcerative colitis and Crohn's disease, the main kinds of inflammatory bowel diseases (IBD).

	Ulcerative colitis	Crohn's disease
Gut wall layer(s) affected	• Mucosa only (except in toxic megacolon)	• Transmural
Extension of the inflammatory process	• By continuity • Starting from the rectum (distal to proximal)	• Segmentally propagated (patchy) • From the oral cavity to the rectum
Characteristic symptom(s)	• Bloody diarrhea (+/- abdominal pain or fever) • Constipation during exacerbations (if only rectum affected) • Moderate weight loss	• Diarrhea • Abdominal pain • Fever • Loss of body mass • Anemization
Local complications	• Rare stenosis • Toxic megacolon • Malignization	• Stenosis • Fistulae • Abscesses • Relapse after colectomy • Perianal lesions • +/- Malignization

Table 2. Mechanisms of gut mucosa inflammation in inflammatory bowel disease (IBD).

Inflammatory mediators (local and systemic increased levels)	**Inflammatory cells (local infiltration) T-cell response:**
Lipid-derived mediators: - Prostaglandins (PGs) - Leukotrienes (LTs) - Endocannabinoids - Platelet activating factor (PAF) **Peptides**: - Cytokines - Interleukins (IL) - Chemokines **Amino acid derivatives**: - Histamine - Nitric oxide (NO) **Reactive oxygen species** (ROS) - Superoxide anion - Hydrogen peroxide **Enzymes**: - Matrix proteases	**Crohn's disease** Th1 response with increased production of: - Tumor necrosis factor (TNF)-α - Interferon-γ (IFN-γ) - IL-1β - IL-6 - IL-12 - IL-17 **Ulcerative colitis** Th2 response with increased production of: - IL-5 - IL-10
Reduced anti-inflammatory cytokines	**Other inflammatory cells**
- Transforming growth factor (TGF)-β - IL-10	- Neutrophils (early stage) - Macrophages (chronic stage)

Table 3. Treatment of inflammatory bowel disease (IBD).

Step-up approach (for mild to moderate IBD):	
Step I	• **Aminosalicylates** (for flare-ups and for maintaining remission in UC, for preventing recurrence after surgery in CD; oral, topical): *sulfasalazine, mesalamine, balsalazide, olsalazine* • **Antibiotics** (for CD if perianal disease or inflammatory mass): *metronidazole, ciprofloxacin*

Step II	• **Corticosteroids** (for acute flare ups):
	  • intravenous *methylprednisolone* or *hydrocortisone*;
	  • oral *prednisone* or *budesonide* (or others);
	  • topical *hydrocortisone* or *budesonide*

Step III	• **Immune-modifying agents** or **immunomodulators** (for refractory disease, for fistulas, and for maintenance of remission if aminosalicylates are not useful):
	  • **Thiopurine agents**: *6-mercaptopurine, azathioprine*
	  • **Anti-TNF monoclonal antibodies**: *infliximab, adalimumab, certolizumab, golimumab*
	  • **Integrin antagonists**: *natalizumab; vedolizumab*
	  • **Other immunosuppresants**: *cyclosporin, tacrolimus, methotrexate*

Step IV	Clinical trial agents (non-approved): • CD: *thalidomide, IL-11* • UC: *nicotine patch, butyrate enema, heparin*
Step-down approach (for severe, refractory disease or dependent on corticosteroids):	
• **Immune-modifying agents**: *thiopurine agents* • **Anti-TNF monoclonal antibodies**: *infliximab, adalimumab*	
Other treatments:	
• **Anti-diarrheal medications**: *fiber supplement (psyllium powder, methylcellulose); loperamide* • **Pain relievers**: *acetaminophen* • **Nutritional supplements**: *iron; vitamin B_{12}; calcium, vitamin D* • **Probiotic agents** (with aminosalicylates) • **Enteral or parenteral nutrition** (CD) • **Tobacco cessation** (CD)	

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; TNF, tumor necrosis factor; IL, interleukin.

Sources (accessed 4th May 2016):

- http://emedicine.medscape.com/article/179037-treatment#d10
- http://www.mayoclinic.org/diseases-conditions/inflammatory-bowel-disease/basics/treatment/con-20034908

Table

Table 4. Reported incidence of Ulcerative Colitis and Crohn´s Disease worldwide in the last ten years.

Country or area	**Ulcerative colitis** (per 100,000)	**Crohn's disease** (per 100,000)
Australia	**17.4**	**19.3**
Canada	**19.5**	**20.2**
China	2.22	1.22
East Europe	4.1	3.1
France	3.2-9.5	4.05-4.9
Iceland	**16.5**	5.5
Italy	7	3.4
Netherlands	3.7-**10**	4.1-6.9
New Zealand	7.6	6.5
Nordic	**12.8-14.8**	5.3-8.6
Puerto Rico	**12.53**	5.89
South Africa	5	2.6
Spain	5.2-**12.5**	5.5-9.03
United Kingdom	**13.9**	8.3
United States	7.6-8.8	6.9-7.9

Figures ≥ 10/100,000 inhabitants are shown in bold.

Table 5. Relationship between diet type, risk of developing inflammatory bowel disease (IBD) and main nutrients/nutraceuticals involved.

	WESTERN DIET	**NON-WESTERN DIET** (i.e, Mediterranean diet)
Rich in	• Red and processed meat • Butter • High-fat dairy products • Eggs • Refined grains • White potatoes and French fries • High-sugar drinks	• Fruits • Vegetables • Legumes • Whole-grain foods • Poultry • Fish
Risk of IBD	Higher	Lower
Main food-derived molecules (nutrients and nutraceuticals) involved	• Monosaccharides • Animal protein • Cholesterol, saturated fatty acids trans fatty acids, linoleic acid, high ratio ω6/ω3 PUFAs • Low fiber	• Complex carbohydrates • Protein-derived bioactive peptides • ω3 PUFAs (DHA, EPA), olive oil, lipid-soluble vitamins (from fish or seeds) • Fiber (soluble and insoluble) = prebiotics • Hydrosoluble vitamins, minerals (i.e., from fruits) • Phytochemicals (flavonoids, polyphenols)

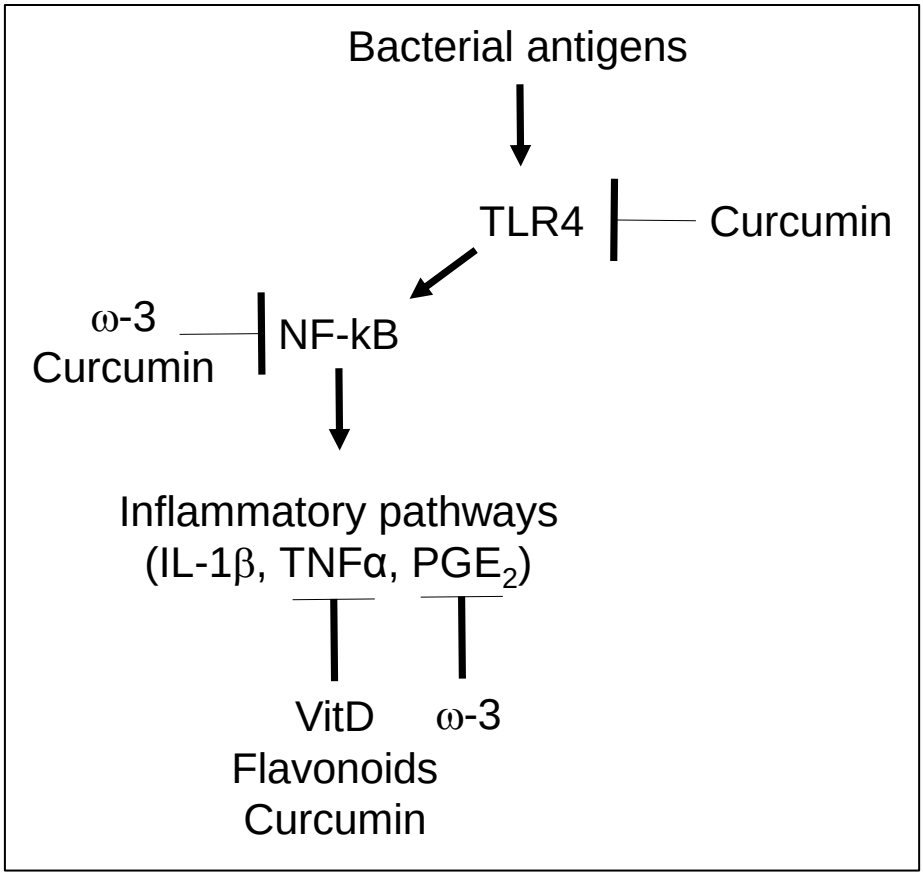
Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PUFA, polyunsaturated fatty acid.

Table 6. Dietary guidance for patients with inflammatory bowel disease (IBD).

Ulcerative colitis	
Active phase	○ Total bowel rest with iv feeding was ineffective = diet has little role in causing UC ○ Low fiber diet
Remission phase or maintenance	○ Low in meat, particularly red meat and processed meat (< 2/week) ○ Avoid margarine; olive oil might be protective ○ Strict avoidance of dairy products and/or lactose is not justified

Crohn's disease	
Active phase	○ Formula-defined liquid diet (enteral nutrition) with appropriate flavoring, and low/no fiber ▪ → Remission of CD in 2/3 patients (first choice treatment in children and adolescents > adults) ▪ 50% patients will relapse within 6 months of return to normal diet ▪ Mechanism is not clear
Remission phase or maintenance	○ Low in animal fat ○ Avoid foods high in insoluble fiber (green beans, corn on the cob, tomato skins, orange pith, potato skins, wheat bran) ○ Avoid processed fatty foods (high in fat and in emulsifiers that alter the behavior of the intestinal lining) ○ Include supplementary vitamin D (up to 1,200 IU/day) ○ Dairy products if tolerated – help ensure adequate calcium intakes

Figure 1. Inhibitory effects of selected nutraceuticals at key pro-inflammatory pathways and effectors.



Abbreviations: IL, interleukin; NF, nuclear factor; TLR, toll-like receptor; TNF, tumor necrosis factor; PG, prostaglandin; VitD, vitamin D; ω-3, omega 3 polyunsaturated fatty acid.