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Review

The role of diet in the prevention and treatment of Inflammatory Bowel Diseases

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Summary. Inflammatory bowel diseases (IBD) – Crohn's disease (CD) and ulcerative colitis (UC) – are chronic conditions characterised by relapsing inflammation of the gastrointestinal tract. They represent an increasing public health concern and an aetiological enigma due to unknown causal factors. The current knowledge on the pathogenesis of IBD is that genetically susceptible individuals develop intolerance to a dysregulated gut microflora (dysbiosis) and chronic inflammation develops as a result of environmental triggers. Among the environmental factors associated with IBD, diet plays an important role in modulating the gut microbiome, and, consequently, it could have a therapeutic impact on the disease course. An overabundance of calories and some macronutrients typical of the Western dietetic pattern increase gut inflammation, whereas several micronutrients characteristic of the Mediterranean Diet have the potential to modulate gut inflammation, according to recent evidence. Immunonutrition has emerged as a new concept putting forward the role of vitamins such as vitamins A, C, E, and D, folic acid, beta carotene and trace elements such as zinc, selenium, manganese and iron. However, when assessed in clinical trials, specific micronutrients showed a limited benefit. Further research is required to evaluate the role of individual food compounds and complex nutritional interventions with the potential to decrease inflammation as a means of prevention and management of IBD. The current dietary recommendations for disease prevention and management are scarce and non evidence-based. This review summarizes the current knowledge on the complex interaction between diet, microbiome and immune-modulation in IBD, with particular focus to the role of the Mediterranean Diet as a tool for prevention and treatment of the disease. (www.actabiomedica.it)

Key words: mediterranean diet, IBD, Crohn Disease, ulcerative colitis, inflammation, nutrition, gut inflammation, micronutrients

Introduction

Inflammatory bowel disease (IBD) has been a global healthcare problem with a sustained increasing incidence over the last decades (1). IBD includes two major forms: Crohn's disease (CD) and ulcerative colitis (UC), which are distinct chronic bowel-relapsing inflammatory disorders. CD causes transmural inflammation and can affect any part of the gastrointestinal tract (most commonly the terminal ileum and the colon) in a non-continuous pattern. CD is commonly associated with complications such as abscesses, fistulas, strictures and perianal involvment. In contrast, UC is characterized by mucosal inflammation and it is organ-specific, affecting only the colon (2). Although the etiology of IBD remains largely unknown, recent

evidence indicates that individual's genetic susceptibility, environment, intestinal microbial flora and immune responses are all factors involved and functionally integrated in the pathogenesis of IBD (3-5). The incidence of IBD has steadily increased in industrialised countries over the 20th century. In developing countries, traditionally considered low-incidence areas, an increasing incidence has been described since the beginning of the 21st century (8-10,14). Studies on migrant populations moving from regions of low incidence to areas with a high IBD incidence point to early life as a key time for environmental triggers (18). In these populations, the second generation, i.e., those born in high-incidence areas, have been shown to have higher incidence rates compared to their parents. More recently, the fast evolving field of epigenetics has offered new explanations on the mechanism by which environmemntal changes induce pathological gene expressions and determine cell phenotype and function in IBD (9). The identification of IBD environmental risk factor remains a subject of intensive research, and diet is one of the best candidates. In fact, diet participates in the regulation of intestinal inflammation, either directly or indirectly by modifying the gut microbiota (6,7). The purpose of this review is to define the role of diet in the pathogenesis and management of IBD, explaining the potential functional role of the Mediterranean Diet in preventing and treating Inflammatory Bowel Disease. The anti-inflammatory potential of Mediterranean Diet is wellknown and established in several other health conditions associated with inflammation. However, the abundance in fibers of this dietary pattern could make it unsuitable for patients with gut inflammation. MD, with appropriate adjustments, is the better dietetic solution in IBD, as indicated by recent evidence.

Gut microbiota and IBD

The microbiota plays a vital role in the health of the host. In fact, it controls the proliferation of pathogenic bacteria present in the intestinal tract (such as *Clostridia* or *Colibacillacea*) (ref. 5,10), stimulates the immune system, regulates the absorption of nutrients (11), regulates the host metabolism and hysiology (12), intervenes in the production of vitamins and enzymes such as vitamin K and biotin6, and in the synthesis of compounds useful for the trophism of the colonic mucosa and required for cell renewal (5,10). Within the gut, the microbiota plays different roles, including the fermentation of amino acids and saccharides, the production of short-chain fatty acids (SCFAs), succinate, ethanol, H2, amines, lactate, phenols, thiolsand indoles, disposal of hydrogen (as acetate H2S andmethane), the degradation of undigested proteins and carbohydrates, and the transformation of bile acids (8). The production of SCFAs, including butyrate and propionateand acetate, plays an essential role in maintaining a healthy mucosa and in the production of anti-inflammatory interleukins (5,11). In brief, SCFAs are derived from the bacterial fermentation of dietary carbohydrates. This fermentation process in carried out in the colon by *Lactobacilli* and *Bifidobacteria* under anaerobic conditions (5). Moreover, butyric acid is the preferred source of energy for colonocytes. Butyric acid has an importantanti-inflammatory effect and controls the proliferation, differentiation and apoptosis of colonocytes. In addition, it strengthens the defensive barrier of the colon by increasing the production of mucin and antimicrobial peptides and by decreasing the intestinal epithelial permeability and increasing the expression of tight junction's proteins (5). Another important function of the microbiota is to keep the concentration of pathogens within limits. This action is accomplished via various mechanisms including direct competition for nutrients, increase of the mucus layer on the intestinal mucosa and through the development and the stimulation of the immune system, particularly of the gut associated lymphatic tissue (GALT) (ref.13). Targeted studies have shown that consumption of large amounts of fat and sugar in the long run, results in a degree of dysbiosis and in a change of microbiota, with increased numbers of *Bacterioides spp* and *Ruminococcus torques (*22).

Any alteration of the bowel eubiosis or in the composition of the microbiota is defined as dysbiosis. IBD is associated with alterations in the composition of the intestinal microbiota, characterised by decreased diversity, reduced proportions of Firmicutes, and increased proportions of Proteobacteria and Actinobacteria (6). Some of the bacterial species with pro-

inflammatory effect are enriched in patients with IBD (Escherichia, Fusobacterium), while anti-inflammatory species (Faecalibacterium, Roseburia) are largely reduced in IBD (6). For example, patients with active IBD have been shown to have a lower abundance of *Clostridium coccoides, Clostridium leptum, Faecalibacterium prausnitzii and Bifidobacterium* (24). Prospective studies investigating the role of microbiome changes on the disease course have been scarce. A Dutch study based on 10 CD and nine UC patients reported patient-specific shifts in the microbial composition, but could not demonstrate general changes in the microbial composition or diversity (25). A Spanish study followed up 18 UC patients over the course of one year; in those who remained in remission *Faecalibacterium prausnitzii* increased steadily, while in those who relapsed it did not (26).

Probiotic preparations contain living bacteria have been suggested to exert positive health effects on the human intestine, modulating mucosal permeability and strengthening the immune system and keeping away pathogens from the intestinal mucosa surface. In particular, animal research has suggested that *Lactobacillus and Bifidobacteria* produce substances which are harmful for Gram-positive and Gram-negative bacteria and compete with pathogenic bacteria (32,38). Moreover, human studies suggested that Clostridium coccodies and C. leptum exert a protective effect against IBD (32). Recently, a meta-analysis based on 22 randomised control trials compared the use of probiotics over 5-aminosalicylates (5-ASAs) and placebo in patients with IBD (40). Overall the meta-analysis suggested that probiotics may be as effective as 5-ASAs in preventing a relapse of quiescent UC. However, the overall efficacy of probiotics in IBD should be confirmed by further research. In addition, long-term benefits of probiotics may be limited without an overall modification of the patient's diet. Thus, single pre-/probiotic administration may not prove useful outside the context of switching to an overall healthy diet plan. Probiotics and other commercial interventions such as tea or berry extracts would be unlikely to counteract an unhealthy diet and, used alone, may, analogous to other medicinal products such as antioxidant supplements, fail to determine primary or secondary disease prevention (41). Dietary composition has shown to affect the microbiota balance; therefore, it is conceivable that altering the diet can have an impact on the inflammatory response (28). In contrast, high-fibre diet regimens increase short-chain fatty acid production by the microbiota and lead to an improved energy expenditure (31). More effort should be put into evaluating complex lifestyle and nutritional approaches for modulating the gut microbiome. Much work remains to be done before understanding whether the effect of dysbiosis in humans reaches that of mice; however, while definitive evidence may be lacking, current evidence strongly suggests that the gut microbiome is a major contributor to human health and the development of disease (32).

Immunity and IBD

The composition of the microbiota depends on several factors including the structure of the host's intestinal epithelium, peristalsis, dietary changes, age, genes, temperature, interaction between different bacterial species, response of the immune system in particular T and B cells, administration of antibiotics, radiations and chemotherapy drugs, and psycophisical stress (5,6,14). Consequently, dysbiosis causes an alteration of intercellular tight junctions that are responsible for keeping the integrity of the intestinal mucosa (15) and its permeability, which is crucial to prevent the access of pathogens (5). The entrance of pathogens determines an activation of the MALT (Mucosal Associated Lymphatic Tissue) and consequently of the inflammatory cascade (leukocytes, cytokines, TNF-α), leading to tissue damage (15). Dysbiosis is also related to the development of a number of diseases including type 2 diabetes mellitus, allergies, fatty liver disease, obesity and IBD (7). There is also discussion on the potential role of heat shock proteins (HSPs) in the pathogenesis of IBD. HSPs are involved in various processes such as folding, translocation and degradation of intracellular proteins under normal and stressful conditions. Being highly conserved molecules with similar sequences in bacterial and human orthologs (molecular mimicry), HSPs can stimulate an immune response, both innate and adaptive, therefore having a role in the autoimmune response (5,21). Several mi-

cronutrients are especially important for immunonutrition, in particular vitamins A, C, D and E, folic acid, beta carotene and trace elements such as zinc, selenium, manganese and iron have gained much research interest. Deficiencies in zinc and vitamins A and D may reduce the natural killer cell function, whereas supplemental zinc or vitamin C may enhance their activity (66,67). Vitamin D has been shown to play a role in the intestinal defence by suppressing the microbial invasion of the epithelium. Vitamin D deficiency has been identified in 82% of IBD patients, compared to the 31% national average, and has been linked to defective epithelial processes. Therapy targeting vitamin D3 signalling was suggested for the treatment of inflammatory diseases, affecting both innate and adaptive immune functions. The overall impact of vitamins on IBD is still not well understood. So far, only two randomised clinical trials were conducted to evaluate the effect of vitamin D supplementation on IBD outcomes. In a Danish study, 94 patients were randomised to receive oral vitamin D3 or a placebo; patients receiving vitamin D3 had a non-significant reduced risk of relapse (68). A more recent Iranian study conducted among 108 IBD patients reported that oral supplementation with vitamin D3 reduced serum TNF-alpha levels, though not substantially (69). In mice, Ananthakrishnan and colleagues demonstrated that a deficiency of vitamin D was associated with an increased risk of colitis, whereas Vitamin D supplementation had an anti-inflammatory effect in mice with colitis, due to the inhibition of pro inflammatory genes such as TNF genes (16). In addition, the intake of PUFA and conjugated linoleic acid (CLA) appears to have multiple benefits in IBD patients because they have anti-inflammatory effects (15). In fact, they decrease the production of interferon-γ and prostaglandin E2 (17) and modify the responsiveness of T cells (15). More studies with larger samples would be beneficial to assess the effect of vitamins supplementation in IBD. The role of trace elements in the prevention and management of inflammatory diseases represent another important field of research. Zinc is involved in the control of DNA replication and transcription and controls signal transduction during T-cell activation (70). Selenium deficiency decreases antibody production, while selenium supplementation enhances T-cell responses and increases antibody synthesis. Selenium is also known to exert antioxidative effects and protection against the deteriorating effects of reactive oxygen species (71). Iron deficiency leads to defective T-cell proliferative response and impaired cytokine production by lymphocytes. It should be noted that iron supports pathogen development and consequently that iron supplementation can also result in an increased susceptibility to infections (72). Of note, dietary iron has also been shown to enhance IBD and carcinogenesis by augmenting oxidative and nitrosative stress. In an experimental animal study, an iron-enriched diet significantly increased colorectal tumour incidence as compared with the control diet (73). Despite the fact that micronutrient deficiencies may theoretically influence the immune system and predispose to the onset and development of IBD, further research is needed to define optimal micronutrient levels and specific therapeutic implications (28). Beyond micronutrients, specific food compounds such as green tea (74-76) or Echinacea (77-79) have also been suggested to reduce or enhance immune stimulation and play a role in IBD prevention.

Epigenetic and IBD

In recent years research has contributed to an improved understanding of the role of epigenetic modifications – i.e., non-coding RNAs and DNA methylation – in defining the molecular basis of IBD (42,43). Such research has been largely driven by observations that genetics alone cannot explain the onset of IBD. Thus, a meta-analysis of GWAS studies estimated that susceptibility loci for UC explained only 16% of UC heritability (44). In this regard, gene-environment interactions have been suggested to play an important role in IBD pathogenesis and this is where epigenetics could offer new insights beyond genetic research (42,45). Epigenetic factors were therefore suggested to mediate interactions between the environment and the genome, thereby providing new insights into the pathogenesis of IBD (46). Earlier studies reported a differential expression of specific microRNAs in the colonic mucosa of IBD patients compared to the mucosa of control patients (43). miRNAs identified in

peripheral blood were additionally suggested as new biomarkers of disease development (47). Recent data showed the implication of miRNAs in the immune response to bacterial invasion and in the differential regulation of cytokines (48). miRNA dysregulation, especially in Th17 cells, has been implicated in IBD. miRNAs have also been shown to regulate the intestinal barrier integrity in UC. As previously reviewed, an increased expression of miR-21 is among the most consistently replicated novel therapeutic targets (47,48). More recently, DNA methylation signatures for UC and CD have been also described. However, whether changes in DNA methylation systematically correlate with gene expression is not clear (49). In addition, it remains a challenge to identify aetiologically significant epigenetic alterations since epigenetic modifications of DNA may differ between tissues, time of development within the same tissue, and environmental influences. Initial evidence arising from epigenetic research is sometimes hard to prove in clinical practice. An example is the identified role of cytokines and subsequent development of biological drugs that fail to prove an important role in disease control. Dysregulation of cytokine genes and increased mRNA levels of cytokines, including interleukin1-beta, interleukin-18 and tumour necrosis factor-alpha (TNFα), were reported in IBD patients compared with controls in the late 1990s (50-53). This led to the introduction of biologically based therapies (i.e., anti-TNFα) in IBD patients. However, predicting drug response and achieving adequate response levels is still difficult in many patients as stand-alone anti-TNFα therapies have not proven completely efficacious in preventing disease progression in many patients (54). Recently, animal models suggested that the lack of response to anti-TNFα could be related to differences in the gut microbiome composition. Thus, alternative strategies are needed to account for the interplay between immunity, epigenetics and dietary factors. Diet is known to influence epigenetic changes associated with various diseases and to modify gene expression patterns in a state of disturbed immunity (45). Poor dietary choices are encoded into the human gut and into the genetic make-up, and could be transferred to the offspring (55). A number of nutrients have been shown to modulate immune responses and may potentially counteract inflammatory processes (56). Recent research suggested secondary plant metabolites, such as polyphenols, may modulate gene expression, chromatin remodelling and DNA methylation (57). Polyphenols in green tea or soybean such as epigallocatechin-3-gallate or genistein have been demonstrated to inhibit DNA methyltransferases activity. Epigenetic effects have also been shown for other dietary components such as curcumin (58). Nutrition provides substrates necessary for DNA methylation and can regulate the activity of the enzymes involved in the one-carbon cycle. Thus, precursors of S-adenosylmethionine, such as methionine, folate, choline, betaine and vitamins B2, B6 and B12, have been suggested to influence DNA methylation patterns (59). Immune cells are rapidly dividing cells and have increased sensitivity to impaired DNA replication. Dietary factors appear to have the potential to modulate inflammation (60). Furthermore, active immunisation against the outer membrane protein of bacteria present in the gut was recently shown to enhance local and systemic immune control via apoE-mediated immune-modulation (61). Immunonutrition was therefore suggested as a less invasive alternative to immunotherapy in protecting against chronic inflammation predisposing to IBD (60). The gut microbiota may alter host histone acetylation and methylation in human colon tissues (62). Fermentation end products, especially short-chain fatty acids such as acetate, butyrate and propionate, which are mostly produced by microbial fermentation of fibres, may be particularly important for the epigenetic regulation of inflammatory reactions (62). A diet poor in fibre leads to a suppression in the microbiota-driven short-chain fatty acid production and to disturbed chromatin effects (62). Of note, the previously mentioned finding that butyrate-producing bacteria (Faecalibacterium) and SCFA-producing bacteria (Roseburia) are decreased in IBD (6). However, the therapeutic role of butyrate-producing bacteria as pharmabiotics in humans has been questioned because of the difficulty of growing them in vitro (63). The current state of research does not allow to make definitive statements on which exact changes in the diet affect epigenetics via the microbiota. Nevertheless, there is accumulating evidence that certain microbes communicate with their hosts by sending out metabolites, influencing gene transcrip-

tion in the colon and potentially driving disease development (see figure 1 online).

Diet and IBD

The Western Diet Pattern

The current diet is considerably different from the traditional diet of previous generations, when the prevalence of IBD was considerably lower. The Western diet pattern is dominated by increased consumption of refined sugar, omega-6 polyunsaturated fats and fast food, combined with a deficiency in fruit, vegetables, and fibers (72). Much of today's food supply has been processed, modified, stored and transported over great distances, in contrast to the traditional diet, where food that was produced locally was consumed shortly after harvest. This shift to the Western dietary pattern is hypothesized to increase pro-inflammatory cytokines, modulate intestinal permeability, and alter the intestinal microbiota promoting a low-grade chronic inflammation in the gut (73). A diet that contains pro-inflammatory foods is an important risk factor in the development of UC. A case-control study carried out in Iran with newly diagnosed UC patients (n=62 UC patients, 124 controls) found that subjects with a higher dietary inflammatory index (pro-inflammatory diet) had an increased risk of developing UC (Odds Ratio (OR): 1.55, 95% Confidence Interval (CI): 1.04-2.32) (23). The authors concluded that encouraging the intake of more anti-inflammatory dietary factors, such as plant-based foods rich in fibers and phytochemicals, and reducing the intake of pro-inflammatory factors, such as fried or processed foods rich in trans-fatty acids, could be a potential strategy for reducing the risk of UC. This was one of the first studies that examined the role of a dietary inflammatory index in the development of UC. Several large scale studies have attempted to elucidate the dietary components that are associated with the risk of developing IBD (22,24,26,27). Overall, these studies suggest that the Western diet pattern is a risk factor for IBD. If we compare the Western diet to Eastern diets based on carbohydrates derived from plants, vegetables, rice and fruits, we note that the Eastern population microbiota has a higher prevalence of *Prevotella spp.* rather than *Bacteriodes spp.* compared to the Western population (8,16). Furthermore, animal sources of protein and fat are associated with a greater number of *Bacteriodes spp.*, while simple carbohydrates and fibers are mostly associated with an increase of *Prevotella spp. (*8,16). On the other hand, while the bacterial fermentation of carbohydrates produces SCFAs that maintains a healthy intestine, the fermentation of protein residues produces metabolites such as organic acids, phenolic compounds, indoles and ammonia, which are deleterious and toxic for the intestine (8). It is demonstrated that diets high in fat and/or sugar destroy the intestinal microbiota, leading to dysbiosis and increased production of endotoxins (23). Dysbiosis modifies the intestinal mucosa, which becomes thinner and more permeable to pathogens and antigens with the consequent establishment a low-grade but persistent, inflammation (22). In contrast, a diet rich in vegetables and fibers reduces the intestinal pH and prevents the growth of potential pathogenic bacteria such as strains of *E. coli* and other *Enterobacteriaceae (*10). In brief, the literature is in support of the fact that the microbiota is intimately related to food quality and that diet influences the composition of the microbiota and represents a source of luminal antigens (15). In a review of 2015, Tomasello and colleagues noted that a Western-style diet may be a trigger for UC and CD (15).

Carbohydrate Intake as a Risk Factor for IBD

A systematic review (n=19 studies with 2609 IBD subjects) reported a negative association between dietary fiber (OR 0.12, 95% CI: 0.04-0.37) and fruit intake (OR: 0.2, 95% CI: 0.1-0.9) and CD risk (22). Soluble fiber from fruit may have a protective effect on CD (24). A high vegetable intake may be associated with a decreased risk of UC (OR range 0.32-0.75) (22). The European Investigation into Cancer and Nutrition study (n=366,351 with 256 incident cases of UC and 117 of CD, and four matched controls per case) reported that an increased consumption of sugar and soft drinks with a low vegetable intake was positively associated with the risk of UC (OR 1.31, 95% CI: 0.85-2.02; p=0.05) (25). An increased consumption of sweets is positively associated with CD (OR:

2.83, 95% CI: 1.38-5.83) and UC (OR: 2.86, 95% CI: 1.24-6.57) (30). Overall, these data suggest that while refined and processed carbohydrates and sweetened beverages are risk factors for IBD, complex carbohydrates including fruit, vegetables and fibers should be included in the diet to improve the management of IBD.

Protein Intake as a Risk Factor for IBD

Similarly, according to Agus and colleagues (22), an excessive consumption of animal proteins is associated with an increased risk of developing CD; while the consumption of fruit and vegetables was inversely related to the risk of CD (15). Patients with CD also showed a shift in the microbiota, with an increase of *Proteobacteria* and *Bifidobacteria* groups, and a decrease of *Firmicutes (*22). For UC, in addition to the large consumption of refined carbohydrates and simple sugars, the consumption of large amounts of fatty acids is also associated with an increased risk of the disease (17). A large prospective cohort study (n=67,581) completed over a 10.5 year period found that a high protein intake, specifically animal proteins (meat, not dairy products) was positively associated with an increased risk of IBD (31). A systematic review (n=2609 IBD patients; 19 studies) reported an association of a high total protein intake with the development of UC (OR range 0.2-3.7) and CD (OR range 0.45-3.34) (22). A high protein intake was associated with a 3.3-fold increased risk of IBD, suggesting that a diet high in animal proteins could be a major risk factor for the development of IBD.

Dairy Intake as Risk Factor for IBD

The European Investigation into Cancer and Nutrition study found that individuals that consumed milk had significantly reduced odds of developing CD (OR: 0.30, 95% CI: 0.13-0.65), suggesting a protective effect of dairy product consumption (28). Individual dairy products consisted of milk, yogurt, and cheese with variable fat content (e.g., full fat, skimmed, semi-skimmed, and unspecified). This is supported by a case-control study in children (n=130 CD patients andn=202 controls) that demonstrated that the consumption of dairy products was not associated with CD (OR: 0.86, 95% CI: 0.42-1.76, p=0.65) (29). Overall, the consumption of dairy products is not a risk factor for IBD.

Fat Intake as a Risk Factor for IBD

There have been conflicting data on the association between dietary fat intake and the development of IBD, as many of the studies are retrospective with small numbers. However, a very large, long-term, prospective study (n=170,805) completed over 26 years did not observe a significant association of total dietary fat intake, saturated fatty acids (SFA) and monounsaturated fatty acids (MUFA) intake with an increased risk of developing CD or UC (26). These findings have been supported by other research studies (74-76). A growing body of scientific evidence indicates that the Mediterranean diet pattern has been associated with significant improvements in health status (77,78) and decrease in inflammatory markers in humans (79). The protective effect is hypothesized to derive from the balance in fats, which includes incorporating MUFA, SFA and fish intake (80). While a few studies show that MUFAs are beneficial in colitis, studies on the effects of SFA and PUFAs on gut health are controversial. Dietary n-6 PUFA, in particular linoleic acid, has been implicated in the etiology of IBD. Dietary n-6 PUFAs are essential fatty acids present in high amounts in red meat, cooking oils (safflower and corn oil) and margarines. A prospective cohort study (n=203,193) conducted over four years found that intake of linoleic acid was associated with an increased risk of UC (OR: 2.49, 95% CI: 1.23 to5.07, p=0.01) (27). Further analysis of the European Investigation into Cancer and Nutrition study (n=260,686) over five years found an increased risk of UC with a higher total PUFA intake (trend across quartiles OR=1.19 (95% CI: 0.99-1.43) p=0.07) (74), which was also supported by a systematic review (n=2609 patients with IBD) that examined pre-illness intake of nutrients and subsequent development of UC (22). A case-control study in CD found that increased total PUFA consumption was positively associated with CD risk (OR: 2.31, 95% CI: 1.12-4.79) (30). The Nurses' Health Study cohorts (n=170,805 women with 269 incident cases

of CD and 338 incident cases of UC) reported that a high, long-term intake of trans-unsaturated fatty acids was associated with a trend towards an increased incidence of UC (HR 1.34, 95% CI: 0.94-1.92) but not CD (26). An increased relative risk of developing IBD has also been associated with a frequent intake of fast foods (fast foods are high in trans-unsaturated fatty acids) (81,82). The relative risk associated with the consumption of fast foods at least two times a week was estimated at 3.4 (95% CI: 1.3-9.3) for CD and 3.9 (95% CI: 1.4-10.6) for UC (82). Frequent fast food intake, defined as more than once a week, was significantly associated with a risk of UC (43%, OR: 5.78, 95% CI: 2.38-14.03) and CD (27%, OR: 2.84,95% CI: 1.21-6.64) (81). It has been speculated that the intake of long-chain n-3 PUFAs (docosapentaenoic acid, eicosapentaenoic acid, docosahexaenoic acid), known as omega-3s, may be of benefit in patients with IBD. The beneficial effects are believed to derive from the anti-inflammatory properties of n-3PUFAs; however, clinical and experimental studies have shown conflicting results (83). Various meta-analyses failed to show a benefit of the supplementation with fish oils in the maintenance of remission in CD and UC (84-86). The dietary intake of n-3 PUFAs was inversely associated with risk of UC, whereas no association has been found with CD (26). The European Investigation into Cancer and Nutrition study (n=203,193) found a negative association of increasing dietary intake of n-3 PUFA, specifically docosahexaenoic acid, with the development of UC (OR: 0.23, 95% CI: 0.06 to 0.97) (27). This is supported by the European Investigation into Cancer and Nutrition-Norfolk study findings (n=26,639)(OR: 0.43, 95% CI: 0.22-0.86) (57). Two case-control studies in CD report that a diet with a regular consumption of fish had a protective effect on the development of CD (OR 0.52, 95% CI: 0.33-0.80,p=0.003) and (OR 0.46, 95% CI: 0.20-1.06, p=0.02) (29,69). The total ratio of n-3 PUFA: n-6 PUFA found in the diet has been hypothesized to be an important issue. One prospective cohort (87) and one case-control study (29) report that a high n-3PUFA:n-6 PUFA ratio in the diet is inversely associated with the risk of IBD. In support of this finding, a dietary intervention trial that focused on increasing the n-3 PUFA: n-6 PUFA ratio was found to be effective in maintaining disease remission in patients with both UC and CD, through increasing n-3 PUFA intake (88). Overall, it does not appear that full fat diets should be avoided. Fat-containing diets rich in olive oil, dairy products and fish but not fish oil pills should be consumed while avoiding large intakes of vegetable oils rich in n-6 PUFA. In summary, several epidemiological studies provide compelling evidence on the role of food in the pathogenesis of IBD. Furthermore, the rise in incidence of IBD in countries that previously had a very low incidence suggests that industrialization and the adoption of a westernized diet may be risk factors for the development of IBD. A reduced consumption of fruits and possibly vegetables, resulting in a reduced overall intake of fibers, with high intake of meats, fast foods and trans-fatty acids appear to be associated with an overall increase in the risk of developing IBD (71).

Dietary Patterns for IBD Management and Prevention

Despite years of research, the role of diet in the prevention and management of IBD is not well understood (80-82). Overall, no effort has been made to provide evidence-based nutritional guidelines for IBD patients and the existing nutritional advice largely follows the principle "If it hurts, don't do it". Dietary recommendations include patient advice to self-monitor and avoid foods that may worsen symptoms, eating smaller meals at more frequent intervals, drinking adequate amounts of fluids, avoiding caffeine and alcohol, taking vitamin/mineral supplementations, eliminating dairy if lactose intolerant, limiting excess fat, reducing carbohydrates and reducing high-fibre foods during flares. Mixed advice exists regarding pre-/probiotics. Recommendations are different across regions/countries. For example, enteral nutrition is recommended for Crohn's disease patients in Japan, which differs from practice in the USA (82). A potential reason for the lack of solid dietary recommendations is the scarcity of studies evaluating the role of diet in IBD (83). So far, only one study has assessed nutritional factors and their influence on disease outcome in newly diagnosed IBD patients (84). In this inception cohort study, a high intake of caffeine

was associated with an increased risk of surgery, a severe disease course and need for higher treatment steps in CD patients; in UC patients, daily fast food intake was associated with an increased risk of surgery and high intake of caffeine was associated with a higher risk of extra-intestinal manifestations. In an attempt to fill this gap, in recent years more effort has been made into evaluating specific diets for the management of IBD, such as the Specific Carbohydrate Diet (SCD) and the low fermentable oligosaccharides, disaccharides, monosaccharides, and polyol (FODMAP) diet. Exclusive enteral nutrition is recommended as a first-line therapy to induce remission in children with active luminal CD (85). In adults, long-term diet interventions such as total parenteral nutrition or an elemental diet have also shown promise (86); however, their administration is complicated and does not allow patients to lead a normal life. The SCD is a dietary regime that aims at inducing and maintaining drug-free remission in patients with IBD, initially developed by gastroenterologist Sidney Haas in 1951 and later popularised by biochemist Elaine Gottschall in the book Breaking the Vicious Cycle: Intestinal Health Through Diet (87). The SCD diet is based on the hypothesis that patients with IBD and other intestinal diseases present a dysfunction of the disaccharidases, which are necessary to digest and absorb disaccharides and amylopectin; therefore, higher amounts of disaccharides would be present into the colon, which may lead to bacterial overgrowth and bowel injury with increased intestinal permeability. The diet allows carbohydrate foods consisting of monosaccharides only (fruit and honey) and excludes disaccharides and most polysaccharides; moreover, it includes vegetables with a high amylose-to-amylopectin ratio, fruits, nuts, solid proteins and fats (87). So far, several case-series studies have suggested an important potential of the SCD diet in the induction and maintenance of remission in IBD 65,88-90). The low FODMAP diet gained much attention in research as a mean for IBD treatment. A recent meta-analysis including two randomised control trials and four before-after studies with a total of 319 patients (96% in remission) reported an overall improvement in gastrointestinal symptoms such as diarrhea, abdominal bloating, fatigue and nausea (91). Recently, plant-based dietary patterns were suggested as valid means of long-term inflammation control (92). Semi-vegetarian diet (SVD) has been shown to exert a preventive effect against IBD relapse in patients who have achieved remission in a prospective, single-centre, two-year clinical trial (95). In particular, the Mediterranean diet has been suggested to exert a strong immunomodulatory effect.

Mediterranean diet in IBD

One diet pattern that is considered useful for the prevention and management of intestinal diseases is the Mediterranean diet. It is characterized by a high intake of fruit and vegetables (rich in fiber, antioxidants and vitamins), olive oil and oily fish (rich in mono and polyunsaturated fatty acids), and whole grains and nuts (15,24). It is based on the daily or weekly consumption of specific food groups according to the standardized food pyramid (24). Current research on probiotics as a food supplement in addition to a mediterranean diet, showed that probiotics (such as *Lactobacillus Rhamnosus*) change the composition of the microbiota, thus allowing the return to eubiosis (5). Prebiotic foods, which contains soluble fibers, have been shown to help in maintaining intestinal eubiosis (25). Prebiotics, for example inulin, are metabolized by the gut microbiota to form SCFAs including butyric acid. Tralongo et al. showed that butyrate had a positive effect on the physiological activity of colonocytes and that it had an anti-inflammatory effect (expressed by reducing the production of pro-inflammatory factors such as Nf-kb) making it a valuable ally in the treatment of IBD (5). Recent data from the Predimed study, a randomised, controlled, parallel trial in high cardiovascular risk volunteers, revealed that over five years the Mediterranean diet was associated with the methylation of genes related to inflammation and exerted high regulatory effects (93). Further intervention trials utilising transcriptomics analyses revealed the potential of the Mediterranean diet in the modulation of gene expression and in the normalization of the microbiota in IBD patients (94). Due to the high amount of fibres, MD can be unsuitable for patients during flares of the disease, but it is highly recommended after remission, with appropriate adjustments. In the following section, each main food of the Mediterranean

diet pattern is considered and adapted to be used in the daily diet of patients with IBD (see figure 2 online).

Pulses

Excellent source of vegetal proteins, minerals (calcium, iron, zinc, phosphate) and vitamins (B1, B9, B3), pulses can be consumed as skinned. Skinned pulses are free from the insoluble metanogenic fraction of their fiber and from anti-nutritive compounds such as phytates, but still contain soluble fibers, vitamins and minerals. Soluble fibers, such as pectin and inulin, do not irritate the gut lining, but still they have a prebiotic action, promoting the growth of microbial species that produce propionic and butirric acid. Propionic and butirric acid exert a high protective action on the gut mucosa, and are often supplemented in IBD patients. In particular, recent works show that butirric acid down-regulates the release of inflammatory cytokines and the activation of nuclear factor kB (34,35 MICI). Another way to consume legumes is to long cook them with their skin, then remove the skin using a sieve. Red decorticated lentils and peas are more digestible than other kind of beans, and are very suitable to recondition the gut.

Vegetables

During remission, vegetables poor of insoluble fibers can be consumed: zucchini, potatoes, carrots, eggplants without skin, green beans, chards. They must be cooked very weel, and consumed as a cream in the first period, then can be consumed whole. In a further stage, raw vegetables can be used: chopped carrots, the inner part of radicchio, fluffy lettuces with little leaves. Greens with a higher content of fermentable fibers, such as cabbage, broccoli, savoy cabbage, artichoke, tomatoes and peppers can be eaten only as cream. A juice extractor can be a very useful tool to eat even vegetables with insoluble fibers, as it is completely removed obtaining a whole raw juice containing enzymes, vitamins, minerals and antioxidant compounds. Recent evidence showed that the soluble fraction of fibers in broccoli prevents relapse in CD patients (36). Thereby a juice extractor can improve the consumption of vegetables in patients with gut diseases.

Fresh fruit

Many studies demonstrate that fruit consumption has a protective immune-modulating effect in IBD (37,38,39) preventing recurrence. The consumption of fruit, which is necessary for the content of natural vitamins, minerals and protective compounds, is possible at every stage of the disease by using a juice extractor. As reported previously, an extractor completely removes the fibres. After remission is achieved with medical treatment, whole fruits can be used: fruit with less fiber at first, such as apple and bananas, orange juice, later small amounts of other seasonal fruits.

Olive oil

Rising studies show that olive oil has a strong anti-inflammatory effect on the gut mucosa (40,41). This effect is due not to oleic acid per se, but to its synergic action with other antioxidants molecules, such as hydroxityrosol, squalen, oleuropein. These components are mainly present in some olive species, such as "coratina" olives, and they are preserved only if the oil is extra virgin obtained by cold extraction. A recent work showed that the synergic effect of dietary olive oil and fish reduces inflammation in IBD patients (42).

Cereals

Cereals, and wheat in particular, have been heavily modified by agricultural technology. Modern varieties of grains are very different from the original cultivar. The gene pool has been modified to select grains with a higher content of gluten, for a better use in panification. Treatment with gamma-rays occurred since 1950, to obtain stronger plants and to ameliorate cooking results. These changes increased the antigenic epitopes, and the related immuno-mediated reactions, with effects on the gastrointestinal tract (43). Ancient varieties of grains, such as Senatore Cappelli (Triticum turgidum durum) or as Enkir (Triticum monococcum, the most ancient cereal raised by man, 7500 b.C.), have not been genetically modified, and have a low immunogenic impact. These grains do not cause inflammation in the gut mucosa (44,45). Bread, pasta and related products made with ancient grains repre-

sent the best choice for patients with IBD. Rice is very indicated in IBD, as it is naturally gluten free, lowering gut inflammation. Whole rice can be consumed after a long cooking.

Bluefish

The grease from bluefish has a widely investigated anti-inflammatory activity, due to its content of omega-3 fats as EPA and DHA (46,47). This Mediterranean food is very appropriated for IBD patients at any stage of the disease.

Nuts and seeds

Less suitable for patients with active IBD, can be part of a daily use even during disease flares if assumed as almond milk. This beverage belongs to ancient tradition of Southern Italy. It can be prepared easily, using only local almonds and water: nuts are soaked over night, then blended. The smoothie is filtered, obtaining a tasty juice suitable for a daily consumption. Almond milk contains only 50 kCal for 100 g; its consumption does not substitutes cow milk, as the latter has a much higher content of proteins, but almond milk has re-mineralizing properties and a high content of unsaturated fats: the amount of oleic acid is similar to olive oil, and linoleic acid is also weel represented. This drink can help patients assuming vegetal omega-3 limiting the fiber intake.

Conclusions

The role of nutrition in the prevention and management of IBD symptoms has been widely demonstrated. There are clear benefits of the mediterranean or vegetarian diets over the western diet. The Mediterranean and vegetarian diets are rich in fruits, vegetables, fish oil, whole grains and olive oil, which provide nutrients such as vitamin D, essential fatty acids, minerals and fibers. These foods maintain a healthy intestinal microbiota preventing dysbiosis, which has been implicated in the pathogenesis of IBD. The role of diet and probiotics supplementation in restoring the balance of the intestinal microbiota and in improving IBD symptoms is well established. Targeted nutrition approaches which take into account the individual genetic make-up and microbiota composition may represent a novel strategy for the prevention and management of IBD.

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