Nutrition in Inflammatory Bowel Disease

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Abstract

Background: Westernization, above all associated changes in diet, has been postulated to be one of the most important factors contributing to the increasing incidence in inflammatory bowel disease (IBD), consisting mainly of Crohn's disease and ulcerative colitis. ***Summary:*** Diet represents a crucially important and intuitively relevant topic for IBD patients. Although a substantial number of patients are prone to follow dietary advice from a variety of sources, including the lay press, there is intriguingly little scientific evidence for such an incitement. This may result in physicians being insufficiently informed about various aspects of nutrition, precluding adequate guidance of their patients with IBD. Importantly, IBD patients are at risk to develop deficiencies in iron, vitamin B12, folic acid, and several micronutrients, which may even be more pronounced in patients with active disease and those following a restrictive diet. This review aims to summarize the latest data from clinical and epidemiological studies investigating diet and its effect on the course of the disease and to outline the most important nutrient deficiencies in IBD patients. ***Key Messages:*** A western diet with an imbalance between omega-6 (n-6)/omega-3 (n-3) poly-unsaturated fatty acids (PUFAs), in favor of n-6 PUFAs, may increase the risk of IBD, whereas a diet high in fruits and vegetables may decrease the risk of IBD. Many approaches to influence the course of IBD with dietary intervention exist. However, to induce or maintain remission in IBD with a change of diet is still in its infancy, and more dietary research is needed before we can apply it in daily practice. Patients with IBD, even in remission, have to be screened regularly for malnutrition.

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Introduction

The change of environmental factors, particularly the westernized lifestyle, combined with an alteration in diet, improved hygiene, vaccinations, increasing use of antibiotics [1], urbanization, and better access to medical supply as increased use of oral contraceptives [2–4], is thought to be one of the main drivers for the rising prevalence of inflammatory bowel disease (IBD) in westernized countries [5–9]. The highest impact of these factors to the development of IBD is probably exerted by the shift to a western diet characterized by high amounts of protein and (unsaturated) fat, but low amounts of vegetables, fibers, and fruits. Furthermore, this "Westernization" of dietary hab-

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its may trigger a proinflammatory environment [10] in susceptible individuals through an alteration in the gut microbiome and a disturbed epithelial barrier function.

Although no guidelines exist advocating a specific diet during established disease [11–14], approximately 70% of IBD patients assume that diet influence their condition [15], nearly 60% of those consider diet to play a major role in triggering a relapse [16], and 16% of them are convinced that diet could initiate the disease [17]. Although IBD patients are highly interested in nutrition, only 8–16% are satisfied about the information they receive from their physicians [18]. Even half of them never received a dietary advice [19]. Interestingly, when trying to modify their dietary habits, patients rather focus on avoidance of certain foods instead of increasing the intake of dietary components with presumably more beneficial properties [20]. Specifically, IBD patients report to avoid spicy foods, vegetables, fruits, nuts, milk, red meat, soda, popcorn, dairy, high-fiber foods, coffee and beans, whereas an improvement of symptoms is rather attributed to banana, rice, and yogurt [21]. Additionally, a population-based Canadian IBD Cohort could show that IBD patients may tend to substitute diets high in nutrients with sugar-laden beverages [22]. This apprehension may not be supportive for IBD patients, but rather fuels the restriction of certain foods in IBD patients with subsequent considerable impact on social life [17] and the potential risk of nutritional deficiencies, including iron, vitamin B12, calcium, and vitamin D [23]. This pattern of avoidance of specific food is even more pronounced in patients with stricturing Crohn's disease (CD) [24], rendering them a highly vulnerable patient group for deficiencies of micronutrients.

In this review, we summarize current knowledge and recent data on IBD and nutrition, highlight dietary components and their potential to modify course of IBD and discuss how to best recognize, treat, and prevent nutrient deficiencies in IBD patients.

Nutrition and Risk of IBD

The worldwide rising incidence of IBD [25] is paralleled by a "Westernization" of dietary habits in developing countries. It is therefore obvious that, in addition to a genetic influence [26], environmental factors, especially diet, undoubtedly play a major role in the development of IBD [8, 9, 27].

The exact pathomechanism how diet promotes the development of IBD is still unknown, while 2 main mechanistic explanations are most prominent and need to be pointed out. First of all, diet has a profound impact on the composition of gut microbiota and changes of nutritional composition during early childhood or even later in life can favor an anti- or proinflammatory composition [28–30]. Western diet is associated with a lower microbial diversity [31], a higher abundance of *Bacteroides and Enterobacteriaceae* [28–30, 32–34], and lower levels of *Firmicutes* [28], whereas a rural diet rather is linked to more short-chain fatty acids and a lower abundance of *Enterobacteriaceae* (*Shigella* and *Escherichia*) [32]. This change in diet in industrialized countries may subsequently shift the microbiota composition, which may promote a proinflammatory environment in susceptible patients.

Previous studies showed that patients with IBD have a lower diversity in their gut microbiota [35, 36] with an increase in invasive *Escherichia coli* [37], increase in *Enterobacteriaceae* family [38], and a reduced proportion of the phyla *Bacteroidetes* and *Firmicutes*. However, it is not clear, whether this dysbiosis represents a primary event triggered by a specific diet or is only a consequence of the disease itself.

Second, aside from microbial alterations, diet can also alter host immunity through many different mechanisms as increased intestinal permeability, decreased level of colonic Treg cells, and increased proinflammatory markers [39]. A western diet high in fat and sugar decreased mucus layer thickness, increased intestinal permeability, and increased tumor necrosis factor α secretion in susceptible mice [40].

There are many potential candidates being responsible for inducing an inflammatory reaction within the gut. Next to protein, lipids, and carbohydrates, also microparticles and food chemicals like emulsifiers or thickeners can contribute to intestinal and potentially subsequent systemic inflammation.

Interestingly, food additives, such as emulsifiers, may simultaneously act on both of the 2 aforementioned mechanisms [41], which will also be eluded below.

Breastfeeding

The first nutrient a human being receives either represents breast milk or formula feeding. The microbiota of infants who are breastfed differ from those who are formula fed [42], and nearly 30% of the bacteria within the gut derive from breast milk [43]. These early perturbations in the microbiome through diet can potentially increase the risk for disease. In the last decades, there has been a decrease in breastfeeding [43] and an increase in IBD [25]. Although this inverse association has not been investigated

systematically yet, it certainly represents an interesting observation that should be further considered. Furthermore, many studies confirm a protective effect against future IBD development in breastfed infants [44, 45], whereas the strongest decrease in risk appears in children fed up to 12 months [46]. Aside from a decreased risk in developing IBD, a history of breastfeeding is inversely associated with a more favorable course in children having CD [47].

Fat

The intake of omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids (PUFAs) are among the most investigated nutrients with a potential association to IBD. n-6, respectively n-3, means that the last double bond is 6, respectively 3, carbon atoms away from the carboxyl end of the polyunsaturated carbon chain of fatty acid. N-6 PUFAs (linoleic acid [LA], arachidonic acid) are precursors to eicosanoids that are proinflammatory, whereas n-3 PUFAs (docosahexaenoic [DHA], eicosapentenoid and alpha-LA [ALA]) are precursors to eicosanoids believed to be anti-inflammatory [48]. LA and ALA are both essential fatty acids and thus have to be ingested, since the human body is not able to synthesize them. In sunflower oil as well as many other plant-based oils and margarine, high amounts of n-6 can be found. In contrary, n-3 can be found in high amounts in fatty fish and cod liver oil (DHA/eicosapentenoid) and also linseed oil and green leafy vegetables (ALA). The change of dietary habits in westernized countries is characterized by a rise of the n-6/n-3 ratio [49].

One of the first epidemiological studies investigating dietary factors and the increase in IBD in Asian countries is a Japanese study that could demonstrate an association of an increased n-6/n-3 ratio and a correlation to an increased incidence of CD [50]. A prospective cohort study [51] revealed a 2-fold increased risk of developing ulcerative colitis (UC) in patients with high intake of the n-6 PUFA LA. Furthermore, this study showed a 77% risk reduction in developing UC in patients with highest dietary intake of DHA acid, a n-3 PUFA. No decreased UC risk in patients eating high amounts of ALA could be demonstrated. Similar to the majority of studies on nutritional intake in IBD, no conclusions can be drawn about the causality of the results because of the study design. Another case-control study in Canadian children with CD demonstrated similar results with a lower risk for CD in children with a higher ratio of n-3/n-6 fatty acids [52]. The protective effect of n-3 fatty acids appears to apply not only in children but also in the adult population over 45 years [53]. In this cohort, total dietary n-3 intake, especially docosahexanaenoic acid, was negatively associated with the development of UC.

These results find support in the prospective Nurses' Health Study cohort, where a higher long-term intake of n-3 PUFA was associated with a lower risk, and the higher intake of trans-unsaturated fatty acids was associated with an increased risk of UC [54].

However, a newer meta-analysis on this subject suggests a lack of association between fat intake and UC risk [55]. On the other hand, and in contrast to many other studies indicating n-3 PUFA as a protective dietary factor regarding IBD risk, a small Japanese case-control study found a positive association of n-3 PUFA and CD risk. The authors argue that the intake of oily fish high in n-3 PUFA would also necessarily increase fat intake as a whole and therefore potentially increase the risk of IBD [56].

To sum up, the currently available data are rather controversial, with most of the studies indicating an increasing risk of IBD with higher amounts of n-6 (or n-6/n-3 quotient, respectively) PUFAs and a possible protective effect of n-3 PUFA [54, 57]. One hypothesis of the inhomogeneous study results regarding fatty acids could be interindividual differences in the metabolism of n-3 and n-6 PUFA. Since dietary fatty acids are metabolized through enzymes that are genetically regulated, a genetic polymorphism at the CYP4F3 locus could modify dietary n-3 and n-6 PUFA beneficially in UC patients [58].

Proteins

Dietary proteins are derived from many different foods and can be classified into plant-based and animal-based protein sources. Evidently, considering the role of proteins in the diet, one has to distinguish between animal and vegetable proteins because animal-based protein sources often consist of more saturated fat than plant-based protein. In the epidemiological analysis of Shoda et al. [50], high intake of animal protein was the strongest independent risk factor for an increased incidence of CD. These findings are confirmed by a recently published prospective study (The E3N Prospective Study) conducted in French middle-aged women [59]. Like in the Japanese study, the positive association between protein intake and the risk of IBD was only seen with regard to animal but not vegetable protein. Other smaller studies and case-control series did show a trend toward a higher risk of IBD in patients, but without statistical significance [60].

However, meat consumption, as a high source of animal proteins, was found to increase the risk of IBD in a

meta-analysis, but this association is ambiguous due to methodological flaws in the included studies [61]. Interestingly, the association of higher risk of IBD could also be demonstrated in high consumption of fish, another source of animal proteins [59, 60].

Carbohydrates

Although the data are inconclusive, most studies show a positive association between high intake of refined sugar and the development of CD [56, 62], but not UC [56, 60]. However, in UC high intake of sucrose, a subtype of carbohydrates may be associated with a higher risk [63]. Despite recently published data [64, 65] showing an increased risk of UC in patients following a dietary pattern high in sugar and sweetened beverages, these findings could not be confirmed by data from 2 large prospective cohort studies from Sweden [66], in which a lack of an association between IBD and sweetened beverages could be demonstrated. However, this study did not distinguish between various artificial sweeteners, such as sucralose, saccharin, aspartame, cyclamate, and other sweeteners. Thus, it still remains possible that distinctive artificial sweeteners may promote the risk for IBD.

Opposed to the possible negative effect of sugars in general, fruits and vegetables, also rich in carbohydrates, may reduce the risk for CD, but not UC [52, 60, 67]. Specifically, many studies analyzed dietary fiber, which is found in high amounts not only in fruits and vegetables but also in whole grain and legumes. In a large prospective study, long-term intake of fiber, particularly from fruits and in a smaller part of vegetables, reduced the risk for CD, but not for UC. In the group with the highest intake (24.3 g/day), there was a 40% lower risk for CD [68]. A meta-analysis could observe a significant dose – response relationship between fiber intake and CD risk with an decreasing risk of 13% for every 10 g/day increment in fiber intake [69]. Interestingly, fiber intake from whole grain or legumes had no effect on the risk for IBD [68]. Another US study showed that patients with great intake of fruits, vegetables, and fish had a 53% lower risk of CD [70].

Another population-based prospective cohort study in Europe (EPIC-IBD) [71] supported the negative association of fiber intake and UC. In contrary to the US data of Ananthakrishnan et al. [68] showing a reduced risk for CD in higher amounts of fiber intake, there was no association seen in the EPIC-IBD study. However, it has to be mentioned that other nutrients in vegetables or fruits may be responsible for reducing the IBD risk [63].

Other Nutrients

While vitamin D deficiency is highly prevalent in patients with established IBD [72], women with high 25-hydroxyvitamin D levels (25[OH]D) were shown to have a significantly lower risk reduction for developing CD. For each 1 ng/mL increase in 25(OH)D plasma level, there could be shown a significant relative risk reduction of 6% for CD and a nonsignificant relative risk reduction of 4% for UC [73]. Another large observational trial (EPIC) did not show an association between prediagnostic 25(OH)D concentrations and the development of CD or UC [74].

Polyphenol with its classes flavonoids (flavonols, flavones, isoflavones, flavanones, anthrocyanidins, and flavanols), stilbenes (resveratrol), phenolic acids, and lignans have anti-inflammatory properties by ameliorating oxidative stress. Despite the potential positive mechanism, the EPIC cohort study [75] could not show a negative association of developing CD or UC and dietary polyphenol intake. Interestingly, flavones, abundant in thyme, rosemary and oregano, and resveratrol, present in grapes and wines, were associated with a lower risk for CD.

In summary, data of macronutrients and IBD risk are very inconclusive, but it can be highlighted that a western diet has a higher risk for IBD [60, 76], and specifically a diet with a high n-3/n-6 fatty acid ratio, rich in fruits and vegetables, reduces the risk of IBD. These statements find support in the latest ESPEN Guidelines [11].

Diet and Course of Disease

Although the association of diet and the development of IBD are highly interesting from an epidemiological and pathophysiological point of view, patients with an established diagnosis of IBD are interested in counseling on dietary modification aiming at ameliorating their disease course. Due to a lack of robust evidence, neither the ECCO, AGA, nor the ESPEN Guidelines recommend any specific diet during remission or active disease. A recently published Cochrane analysis concludes that an effect of any dietary interventions on CD or UC is uncertain [77]. Therefore, physicians are reluctant to provide any specific recommendations. Subsequently, the majority of patients continue their seek of dietary advice in various sources, including the Internet [78], where the quality and evidence basis of advice received hardly can surpass physician-based counseling. Thus, it is crucial that physicians are capable of providing certain dietary recommendations to patients and give orientation in the best possible way despite the clear-cut limitation of data. Three

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quarters of patients avoid – presumably unnecessary in the majority of instances – certain foods during remission to prevent a flare [16]. Even more patients avoid some food groups, especially proteins and fat, during flares due to fear of worsening symptoms [19, 79].

Regarding dietary modification, patients can either omit certain foods (elimination or exclusion diets) or add specific nutrients to the diet. It is crucial to differentiate between diets that may induce or maintain remission and consequently impact the course of disease and diets that only alleviate symptoms of IBD patients.

Elimination/Exclusion Diets

To explain the effect of exclusive diets, various mechanisms are currently being discussed. Some of the hypotheses feature a direct relationship between diet and IBD. For example, it has been suggested that diet can directly alter the composition of the microbiome. Other mechanisms suggest that dietary antigens trigger an immune response and finally diet influences the production of metabolites by the microorganisms living in the gut, which could have an impact on the mucus layer and the immune response [80].

Exclusive enteral nutrition (EEN) is the only really established diet in IBD patients, specifically in pediatric CD patients [81, 82]. Enteral nutrition, classified as elemental (based on amino acids, sugars, fats, vitamins, and minerals) or nonelemental (composed of oligopeptide or whole-protein sources), is a liquid diet given by mouth or by feeding tube. Due to remission rates up to 80% in pediatric CD patients [83–85] following 6–8 weeks of EEN and a better efficacy and higher mucosal healing rates than corticosteroids [86], exclusion diet is considered as first-line treatment option in children with active luminal CD [87]. Similar remission rates can be achieved regardless of whether elemental or nonelemental regimens are used [81]. In adult CD patients, EEN is less effective than corticosteroids in inducing remission [81]. Furthermore, its poor palatability is the main reason for an exceedingly rare use in the adult population, and ECCO does not recommend EEN as therapy for inducing remission in adult CD patients [13]. However, in contrast to Europe, in Japan, EEN is used as primary therapy in adult CD patients [88] due to a Japanese study demonstrating higher rate of inducing remission and a better safety profile [89].

Due to the fact that partial enteral nutrition (PEN; only 50% elemental formula) reduces markedly the efficacy of inducing remission [90], the exclusion of all nutritional components representing a regular diet is probably the main mode of action in EEN.

There are insufficient data to use EEN as a maintenance therapy in adult or pediatric quiescent CD patients [91]. However, a small Japanese randomized-controlled trial showed a lower relapse rate in patients assigned to a half elemental diet than that in the free diet group (34.6 vs. 64.0%, multivariate hazard ratio 0.4) [92]. Additionally, there exists no indication in treating UC patients with EEN.

The Crohn's Disease Exclusion Diet (CDED) consists of a reduced intake of animal and saturated fat, gluten-containing grains, and emulsifiers, and an increase in fruits, vegetables, and resistant starch. Fifty percent of nutrition will be given as PEN. The reduction of dietary components is the most important mechanism, with allowed nutrients serving to reduce possible nutrient deficiencies and improve dysbiosis. The first study investigating CDED confirmed its effectiveness for the induction of remission in children with CD [93]. A further study demonstrated an induction of remission even for children failing biological therapy [94]. The data of the first randomized controlled study comparing CDED plus PEN versus EEN over 12 weeks in pediatric CD patients demonstrated similar response and remission rates by week 6 and sustained remission by week 12 [95]. Due to the easier treatment approach with the same efficacy, CDED has the potential to change the dietary recommendation in the future. There is an ongoing study with adult CD patients following CDED [96].

A novel diet, called CD-TREAT diet, tries to mimic EEN with an ordinary food diet, based on the composition of EEN [97]. The diet excludes specific components like gluten and lactose and is low in fibers. The advantage of the CD-TREAT diet to EEN is the palatability that is the limiting factor of EEN in adults. The study demonstrated a better tolerance of CD-TREAT in a healthy population and induced a similar effect to EEN on the fecal microbiome. After 8 weeks of CD-TREAT diet, 80% (4/5) showed a clinical response and 60% (3/5) of the pediatric CD patients were in remission. A limitation certainly is the low number of only 5 active pediatric CD patients. Nevertheless, this novel approach in creating a diet based on the established EEN is interesting and has the potential to influence further dietary interventions.

The specific carbohydrate diet (SCD) is based on an exclusion of complex carbohydrates and processed foods. Monosaccharides, chicken, fish, and hard cheese are allowed. It is believed that complex carbohydrates are poorly absorbed in the intestinal tract and therefore result in inflammation. Only case series and small retrospective studies investigated this type of diet. In pediatric CD pa-

tients, a symptomatic improvement could be demonstrated [98] as well as a mucosal improvement [99]. Another uncontrolled study showed a lack of mucosal healing with SCD in asymptomatic children with CD [100]. Recently, a small prospective study with 12 pediatric CD patients showed an improvement in clinical and laboratory parameters and changes in the fecal microbiome [101]. In adult patients, a clinical benefit could be shown through an online survey [102] and a case series of patients in remission following an SCD [103]. No studies in adults investigated laboratory or mucosal improvement.

Vegetarian diet is thought to presumably downregulate inflammation, whereas the western diet is proinflammatory and leads to dysbiosis [104]. Around 4% of IBD patients follow a vegetarian diet [19, 105], whereas 17% of them restrict their diet due to belief of a benefit for their IBD [105]. A prospective cohort study investigating dietary factors in UC patients in remission could demonstrate that a higher intake of meat, particularly red meat, could increase the risk of a relapse in UC [106]. A Japanese study with 22 CD patients in remission showed after 2 years a higher maintenance of remission in the semi-vegetarian diet (94%) than in the omnivorous group (33%). The semi-vegetarian diet consisted of a lacto-ovo-vegetarian diet with once-weekly fish and meat once every 2 weeks [107]. However, a cross-sectional analysis in Swiss IBD patients did not find an association of vegetarian diet and the course of IBD [105]. In a recently published prospective randomized trial (Food and Crohn's Exacerbation Study) [108], a reduced consumption of red meat and processed meat did not reduce the risk of symptomatic CD relapse in patients in remission. In addition, calprotectin was measured in a subset of patients, which showed no difference between the 2 groups.

Aside from a lower intake of protein or fat, vegetarians normally eat more vegetables and fibers than omnivores. In a mouse model, dietary fat induced colitis in interleukin-10-deficient mice, so that the authors conclude that certain fats may in genetically susceptible hosts promote IBD [109]. A recently published prospective study in UC patients found a 3-fold increased risk of flare in patients consuming specific fatty acids like myristic acid (contained in palm and coconut oil and dairy fat) as well as in patients consuming ALA [110]. This finding may appear surprising as ALA belongs to the n-3 PUFA, which are thought to act anti-inflammatory [48]. However, there exists only one study showing a positive effect of n-3 PUFA regarding the course of disease in IBD. In patients with CD, a fish-oil preparation containing a high dose of n-3 PUFA reduced the risk of a flare compared to patients receiving placebo capsules significantly with a 33% absolute reduction (28 vs. 69%, $p < 0.001$) [111]. The results of this study were questioned because of the small sample size (78 patients). In a larger multicenter trial (EPIC-1 and EPIC-2) with >1,000 patients with CD n-3 PUFA did not reduce the risk of a flare over 1 year of follow-up [112]. A recently performed meta-analysis came to the same results as the EPIC studies, namely, that in IBD n-3 PUFAs have, despite the anti-inflammatory effect within the gut [113], no effect in maintaining remission [114].

A study by Llewellyn et al. [115] examined over 30 different diets in mice and demonstrated that a high-protein diet exacerbates colitis in mice and dietary psyllium, a specific fiber, ameliorated colitis, was associated with an increased bacterial diversity and reduced intestinal permeability. The authors propose that in mild to moderate IBD, a diet low in protein and high in selectively beneficial fiber could improve intestinal barrier function and reduce the microbial load. Furthermore, a study by Brotherton et al. [116] demonstrated a 40% reduced flare risk in patients with CD who did not avoid fiber than in patients who avoided high-fiber diet. In UC, no difference could be shown. Patients with UC consumed more fibers than patients with CD; especially, female CD patients and CD patients with prior surgery and hospitalization consumed significantly less fibers. This may partly be due to conscious avoidance of fibers by CD patients with strictures due to fear of obstructive symptoms or because of recommendation of their treating physician. These results are in contrast to a systematic review conducted by Wedlake et al. [117], in which no effect of inducing remission or avoidance of flare regarding fiber intake in patients with CD could be shown. Avoidance of dietary fibers during a disease relapse represents a generally accepted recommendation [118]. Interestingly, a recently published trial investigating the risk for pouchitis and fruit consumption [119], a source high in fibers, could show a lower rate of pouchitis in UC patients consuming high intake of fruits. Furthermore, a higher microbial diversity in patients with high fruit consumption was found.

The Paleo diet, also referred to as the "Stone Age diet," is based on the concept that the nutrition of our ancestors was more natural and therefore healthier. It contains vegetables, fruits, nuts, seeds, small fish/shellfish, lean small game meat, and avoidance of processed foods [120]. An extension of the Paleo diet is the autoimmune protocol diet in IBD. This diet was investigated in an open-labeled uncontrolled trial with no improvement in inflammatory markers, but an amelioration of symptoms and a maintenance of remission in all 11 patients [121].

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A similar anti-inflammatory diet with avoidance of lactose and processed complex carbohydrates, a higher intake of soluble fiber, leeks, onions, and fermented foods (pre- and probiotics), and a modified fat intake has been demonstrated to ameliorate symptoms in IBD patients in case series [122].

Although a Mediterranean diet is known to have beneficial effects on multiple chronic diseases [123, 124], with anti-inflammatory effects [125] and microbiota-modifying properties in CD patients [126], no randomized trial yet has systematically addressed Mediterranean diet in IBD. However, a randomized trial in UC patients is currently ongoing [127].

Fermentable, oligo-, di-, mono-saccharides, and polyols (FODMAPs) are poorly absorbed short-chain carbohydrates that may trigger abdominal bloating, abdominal pain, wind, and diarrhea. IBS-like symptoms are common in IBD and affect around 39% and are more common in CD than in UC [128], and differentiating these symptoms to inflammation-related pain can be cumbersome and difficult.

A reduction of FODMAPs improved abdominal pain, bloating, and diarrhea in around a half of IBD patients [129]. Furthermore, a randomized, double-blind, placebo-controlled study in patients with IBD and IBS showed greater severity of pain, bloating, flatulence, and fecal urgency in patients consuming FODMAPs [130]. It is important to mention that a diet low in FODMAPs may improve symptoms in IBD patients but does not affect the inflammatory activity.

Interestingly, gluten-free diet is followed by around 5% [105, 131, 132] of IBD patients without celiac disease that is more than the double compared to the general population [132]. Almost half of the patients believe that this diet has a beneficial effect on their disease [105], although there are no studies showing that the inflammation would be positively influenced other than a clinical improvement [131]. Furthermore, the amelioration of abdominal symptoms in nonceliac gluten sensitivity presumably is more related to the avoidance of fructan rather than gluten [133], so that a low FODMAP diet seems to have a higher impact regarding symptoms than a gluten-free diet.

To complicate this topic even further, emulsifiers are used in many diets that could alter the gut microbiota and promote colitis [41, 134]. This effect appears to be directly related to a microbiota-modulating property of some emulsifiers, as in unexposed mice undergoing fecal microbiota transplantation with stool from previously exposed mice, alterations in mucosal barrier could be induced. Titanium dioxide nanoparticles contained in pharmaceutical products represent another food additive, which has been shown to promote intestinal inflammation in dextran sodium sulfate colitis in mice [135]. Furthermore, splena, an artificial sweetener consisting of sucralose maltodextrin, promotes in CD-prone mice an alteration of the microbiome with *E. coli* overgrowth and increase of *Proteobacteria* what consecutively resulted in elevated myeloperoxidase activity and increased inflammation and gut damage [136].

We can summarize that there exist several dietary options to influence symptoms in IBD patients and diets that may alter the course of IBD. Patients who are interested in a special diet should, however, be advised by an IBD specialist or dietician due to the risk of malnourishment or nutritional deficiencies.

Dietary Supplements
ECCO's topical review on complementary medicine and psychotherapy in IBD [137] concludes that there is insufficient evidence to support the use of vitamins to induce or maintain remission in CD and UC.

Nevertheless, a prospective cohort study demonstrated that UC patients with 25(OH)D levels below 35 ng/mL had a higher risk of clinical relapse (OR 1.25, 95% CI 1.01–1.56, $p = 0.044$) [138].

In CD patients, 25(OH)D concentration is inversely associated with disease activity [139], and in UC patients, 25(OH)D concentration is inversely associated with mucosal inflammation [140]. Moreover, a longitudinal study demonstrated higher morbidity and disease severity in patients with low 25(OH)D levels [141].

Furthermore, oral supplementation with 1,200 IE vitamin D3 reduced the risk of relapse in CD patients insignificantly from 29 to 13% ($p = 0.06$) [142]. Another study showed similar results, in which the quality-of-life scores improved and the CDAI score decreased after vitamin D supplementation, but there were no significant changes in laboratory or cytokine measures [143]. Additionally, a vitamin D substitution with 40,000 units cholecalciferol weekly for 8 weeks in active UC patients reduced intestinal inflammation and increased the abundance of *Enterobacteriaceae* without altering the fecal bacterial composition [144].

Although the data are not very robust, supplementing vitamin D is safe and well tolerated, so that it should be given to all IBD patients with vitamin D deficiency [145].

Anthocyanins, which occur in high amounts in blueberries and black raspberries, have anti-inflammatory and antioxidative effects [146]. An open pilot trial demonstrated that a daily standardized anthocyanin-rich bil-

berry preparation in mild to moderate UC patients achieved remission and response in 63.7 and 90.9%, respectively, after 6 weeks. Additionally, goji berry, another traditional supplement, has been shown to promote butyrate-producing bacteria and *Bifidobacteria* in interleukin-10-deficient mice, which in turn results in the suppression of intestinal inflammation [147].

Another trial investigating antioxidative properties could demonstrate a significant reduction of oxidative stress in CD patients receiving vitamin E and C supplementation. However, disease activity remained stable [148]. Aloe vera, an herbal preparation with potential anti-inflammatory effects in vitro [149], showed a significant clinical response compared to placebo (47 vs. 14%, $p < 0.05$) in a double-blind, randomized, placebo-controlled trial but no significance in terms of clinical remission (30 vs. 7%, $p = 0.09$) or improvement (37 vs. 7%, $p = 0.06$) after 4 weeks [150]. Another antioxidant is quercetin, a flavonoid that is present in vegetables and fruits. Quercetin could ameliorate colitis in mice by inducing anti-inflammatory effects of macrophages and could restore hemostasis of the microbiota in colitic mice [151]. This interesting approach should be further studied.

A further herbal treatment consisting of myrrh, chamomile blossom extract, and coffeae carbo was studied in a randomized double-blind trial in quiescent UC patients compared to mesalamine [152]. The relapse rates after 12 months did not differ between the 2 groups, rendering the German Society for Digestive and Metabolic Diseases to advocate its use as complementary treatment in UC maintenance therapy [153].

Curcumin, a polyphenol derived from the Indian spice turmeric (Curcuma longa), is used in traditional Chinese medicine and in ayurvedic medicine because of its anti-inflammatory and antioxidative properties [154, 155]. In a randomized, placebo-controlled, double-blind study, curcumin in a dose of 3 g daily was more effective than placebo in inducing clinical remission and response in mild to moderately active UC despite maximal mesalamine treatment (53.8 vs. 0%, $p = 0.01$ and 65.3 vs. 12.5%, $p < 0.001$, respectively) [156]. All patients continued their optimal mesalamine medication. The study has been criticized for not adequately being blinded because of the potential smell and taste of curcumin [157]. Besides an effect in inducing remission, curcumin has been shown, even in a lower dose of 2 g daily, to maintain patients with quiescent UC in remission [158]. In this randomized, double-blind, placebo-controlled trial, only 4.7% patients who received curcumin relapsed during 6 months of therapy compared to 20.5% in the placebo group ($p = 0.04$). There

were no serious side effects. Furthermore, curcumin may be effective as enema in UC patients. In a pilot study, patients receiving curcumin enema had higher clinical response (92.9 vs. 50%, $p = 0.01$) and were significantly more in remission (71.4 vs. 31.3%, $p = 0.03$) than patients receiving placebo enemas (significant only in the per-protocol analysis). A Cochrane analysis supports the finding that curcumin is effective in the maintenance of remission in UC [159].

For the daily use of curcumin, 2 important facts have to be mentioned. First, the acceptable daily intake evaluated by the FAO/WHO Expert Committee on Food Additives (JEFCA) [160] is 0–3 mg/kg bodyweight, being considerably lower than the doses used in the studies. Second, due to the fact that curcumin is not labeled as a medication and only available as over-the-counter food supplement, it is often not available in pure forms and contains numerous additives. Those capsules frequently available represent turmeric capsules with around 50 mg of curcumin and piperine, which will enhance serum concentration of curcumin [161]. This makes it very difficult to achieve the high doses used in the studies.

Plantago ovate (Psyllium) is a dietary fiber indigenous to Mediterranean region and India and used as herbal medicine [162]. In an open-label trial with 105 UC patients in remission, subjects were randomized in groups receiving Plantago ovata seeds (10 g b.i.d.), mesalamine (500 mg i.d.), or Plantago ovate seeds plus mesalamine [163]. There was no difference in maintenance of remission between the groups, so that the authors concluded that Plantago ovata might be as effective as mesalamine to maintain remission in UC. Furthermore, the fecal butyrate level was significantly increased in patients who received Plantago ovata.

Malnutrition

Patients with active IBD are at an increased risk of malnutrition. The prevalence of malnutrition in IBD ranges between 6 and 16%, representing a 5-fold increase in risk for malnutrition as compared to non-IBD subjects [164, 16]. Regardless of the proper definition used for malnutrition, the high prevalence calls for a more profound consideration of this complication among healthcare professionals. Unjustified bowel rest during hospitalization may further worsen the situation in UC patients [165]. History of surgery due to IBD doubles the risk for malnutrition, while ongoing clinical activity and avoidance of some food groups during a flare is associated with

a 4- and even 10-fold higher malnutrition risk, respectively [16]. Therefore, the highest impact on malnutrition probably is derived by food-restrictive behavior and decreased appetite during flare.

The most common micronutrient deficiencies in descending order are iron, vitamin D, vitamin B12, zinc, and folic acid deficiency. Cause of micronutrient deficiencies are multifactorial and include a restricted food intake, enteric loss of vitamins, malabsorption, and undesirable effects of some medication [166].

Iron Deficiency

Prevalence of iron deficiency (ID) can be seen in up to 70% and is the most common reason for anemia in IBD patients (ID anemia [IDA]). The second most common cause of anemia in IBD patients is anemia of chronic disease (ACD) and often co-exists in IBD patients with ID. ID in IBD patients is multifactorial and results from a decreased intake of iron, an impaired iron uptake in the duodenum and upper jejunum, decreased iron resorption due to high hepcidin levels, and chronic blood loss from the inflamed mucosa [167]. Furthermore, in CD, low BMI and nonsmoker are positively associated with IDA [168].

Diagnosing IDA in IBD patients can be difficult due to the overlap of ACD in many patients. Normally, a ferritin <30 μg/L is unequivocally diagnostic for an ID, whether with or without anemia. As ferritin acts as an acute-phase reactant in inflammatory states, as well as in obesity, age, and liver disorders, ferritin level rise and can therefore mask ID. However, ferritin levels >100 μg/L exclude an ID even in states of inflammation [169, 170]. In cases of ferritin values between 30 and 100 μg/L with elevated CRP, transferrin saturation can be measured. A transferrin saturation <20% implies an absolute or functional ID. Absolute ID is defined as transferrin saturation <20% with a ferritin <100 μg/L and functional ID (major component of ACD) as transferrin saturation <20% in combination with ferritin concentrations of 100–299 μg/L [171, 172].

In treating iron-deficient IBD patients, some aspects have to be considered. The well-known Ganzoni formula underestimates iron requirement in IBD patients, why a new simplified and more accurate dosage scheme for IBD was evolved (FERGIcor) [173].

The widely used oral iron supplements consist of iron salts (iron sulfate, fumarate, and gluconate), and the absorption of nonheme iron is poor. The duodenum can maximally absorb 10–20 mg of iron per day and around 90% is not absorbed [174]. Therefore, high doses are often administered, what may lead to ROS-mediated toxicity of nonabsorbed iron on intestinal mucosa [175]. Further-

more, oral iron can reduce *Lactobacillus* and *Bifidobacterium* bacteria and increase abundance of *Enterobacteriacea* [176] and subsequently lead to gut dysbiosis and increase inflammation and diarrhea [177, 178]. Other small studies confirmed the potential of an increased clinical disease activity in IBD patients after oral ferrous fumarate [179] and a small, but in our opinion, a relevant chance of having a relapse of 6% [180].

Due to the abovementioned concerns and high rates of gastrointestinal intolerability to oral ferrous iron, a novel oral iron comprising a stable complex of ferric iron with maltol, namely, ferric maltol, has been tested in IBD patients in a Phase 3 trial [181]. The Phase 3 extension trial confirmed the tolerability of ferric maltol [182].

Nevertheless, oral iron cannot be completely abandoned in IBD patients, but it has to be kept in mind that high doses of oral iron should be avoided in IBD patients, especially in some general vitamin supplements. If given orally, iron should be administered on alternate days in low single doses to optimize iron absorption [183].

Due to high hepcidin level resulting from inflammation [184], oral resorption of iron may be severely hindered or even be impossible in active IBD patients. Therefore, ECCO recommends intravenous iron in clinically active patients, in patients with intolerance to oral iron, or those in need of erythropoiesis-stimulating agents and in case of hemoglobin levels below 10 g/dL (due to much faster response of intravenous iron) [185].

Administration of intravenous iron may increase the risk of infection to around 33% compared to oral or no iron [186]. Therefore, in patients with ongoing infection, intravenous iron therapy should be only given after careful risk versus benefit consideration due to a fear of exacerbating the infection [187].

After correction of ID, every patient should control iron levels every 3 months for at least 1 year, and if ferritin drops below 100 μg/L, iron should be substituted [185]. Patients with active disease should be screened every 3 months and patients in clinical remission every 12 months regardless of anemia or not [188].

Vitamin B12 Deficiency

The prevalence of vitamin B12 ranges between 6 and 38% [189] due to different diagnostic methods used. A true vitamin B12 deficiency in asymptomatic patients is defined as a serum cobalamin <148 pmol/L (200 ng/L) and an elevated serum homocystein or methylmalonic acid [190]. In the duodenum, dietary cobalamin binds intrinsic factor, synthesized by the parietal cells, for its absorption in the terminal ileum [191]. Since CD can affect

the entire gastrointestinal tract, a vitamin B12 deficiency is much more frequent in CD than in UC patients [168]. The main risk factor for vitamin B12 deficiency is an ileal resection >30 cm [189]. Interestingly, despite being the main site of cobalamin absorption, an ileal CD is not a risk factor for a cobalamin deficiency [189]. A well-conducted prospective observational study in which besides cobalamin also methylmalonic acid was measured could demonstrate that a true vitamin B12 deficiency is very rare (3% in CD and 3.3% in UC). Normally, UC patients have a vitamin B12 deficiency in a similar frequency as the general population. An exception is UC patients with ileo-anal J-pouch that may suffer of a vitamin B12 deficiency, probably due a small bacterial overgrowth [192]. Anecdotally, after many years of backwash ileitis, a vitamin B12 deficiency could result. However, this has never been investigated.

Vitamin D Deficiency

Up to 60% of IBD patients have a vitamin D deficiency, especially patients diagnosed with CD and an increased disease activity [72, 193, 194] or pregnant women with IBD [195]. Interestingly, young male patients have a very high risk [141] and CD patients with isolated colonic involvement or UC patients had a similar prevalence of 25(OH)D levels compared to CD patients with ileocolonic or small bowel disease [141]. Additionally, a meta-analysis could demonstrate a higher prevalence of vitamin D deficiency in patients with IBD compared to healthy patients [196]. The underlying reasons for vitamin D deficiency in IBD are multifactorial. There are 2 natural sources of vitamin D, namely, ergocalciferol (vitamin D2), being present in food, especially in fatty fish and mushrooms, and vitamin D3 synthesized in the epidermis of the skin upon UVB irradiation [197]. Since in most northern countries vitamin D deficiency is a common problem in the general population, malabsorption of vitamin D is probably not a major causative factor for the vitamin D deficiency in IBD. Rather, patients with IBD have an insufficient exposure of sun and the inflammation upregulates cytokines that subsequently reduce the serum 25(OH)D level [197].

Although the data regarding a potential benefit for the course of disease in IBD are inconclusive, vitamin D is important to bone health. Especially in patients with IBD, who probably needs repetitively corticosteroids, low 25(OH)D levels should be avoided. Since adherence is an important limitation in patients with chronic diseases, a practical approach to substitute vitamin D is giving them 1 monthly 45,000 IU.

Zinc Deficiency

Zinc is a trace element found in high amounts in food of animal origin, especially in oysters and beef [198]. It is not surprising that vegetarian have much more often a zinc deficiency than omnivores [199]. Due to the fact that zinc is absorbed in the small intestine and the main route of zinc losses are endogenous intestinal losses with up to 12 mg zinc loss in patients with a stoma [200, 201], patients with malabsorption are prone to zinc deficiency. In a Korean study, zinc deficiency could be demonstrated in 38.5% of IBD patients [202]. Likewise, around 65% of CD patients in remission were found to have zinc levels below the reference value despite a higher intake than the controls [203]. In children with CD, zinc deficiency is not very frequent but higher than in the healthy controls [204]. The low zinc values are associated with an increased risk for hospitalization, surgery, and complication in CD and UC [205], and normalization of zinc deficiency was associated with these outcomes [205]. Although low zinc levels did not predict a complicated disease course in the Swiss IBD Cohort, it was associated with depressive symptoms in multivariate analysis [206]. However, serum zinc levels are notoriously difficult to interpret because inflammation, collection time during the day, age, and sex may influence zinc concentration [207]. Therefore, it is debatable if serum or plasma zinc values represent zinc status adequately [200, 208]. Nevertheless, despite its inaccuracy, plasma zinc level is probably nowadays the best indicator measuring zinc status [209]. Another way to asses zinc status would be clinically, whereas the clinical syndrome of acrodermatitis enteropathica with red, desquamating lesions on the hands and the nasolabial folds together with hair loss is pathognomonic for zinc deficiency [208].

As zinc interferes with the intestinal absorption of iron, especially copper, oral supplementation should not be carried out for longer than 2–3 weeks [210, 211].

Conclusion

Western lifestyle, specifically western diet, is a major driving factor for the increased prevalence of IBD in industrialized and emerging countries. Increased intake of fats and/or proteins, reduced intake of fruits and vegetables, as well as the increase in the use of emulsifiers or other binding substances are among the most important candidate factors to promote inflammation in the intestines of healthy subjects. However, as of today it remains unclear which of these individual nutritional factors are

primarily responsible for the recent epidemiological increase in IBD.

Although there are countless books and websites on nutrition and IBD, there is little evidence to support restrictive dietary interventions in patients with IBD. Therefore, current recommendations to our patients should center around and encourage a healthy and balanced diet based on unprocessed foods instead of restriction and/or supplementation of specific dietary components.

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Author Contributions

P.S. conception and design of the study, drafting the article, approved the final version. M.M.-G., D.S., S.R.V., and H.T. design of the study, critical revision, and approved the final version. L.B. concept and design of the study, critical revision, and approved the final version.

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