

Diet and nutritional factors in inflammatory bowel diseases

Danuta Owczarek, Tomasz Rodacki, Renata Domagała-Rodacka, Dorota Cibor, Tomasz Mach

Danuta Owczarek, Renata Domagała-Rodacka, Dorota Cibor, Tomasz Mach, Department of Gastroenterology, Hepatology and Infectious Diseases, Jagiellonian University Medical College, 31-531 Cracow, Poland

Tomasz Rodacki, Department of Food Chemistry and Nutrition, Jagiellonian University Medical College, 30-688 Cracow, Poland

Author contributions: Owczarek D and Rodacki T designed the paper, searched and analyzed the literature, drafted and revised the paper, approved the final version; Domagała-Rodacka R wrote the tables, drafted and revised the paper, approved the final version; Cibor D and Mach T searched and analyzed the literature, drafted and revised the paper, approved the final version.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Danuta Owczarek, MD, PhD, Department of Gastroenterology, Hepatology and Infectious Diseases, Jagiellonian University Medical College, Kraków, 5 Śniadeckich St., 31-531 Cracow, Poland. owczarek@su.krakow.pl
Telephone: +48-12-4247340
Fax: +48-12-4247380

Received: June 26, 2015

Peer-review started: June 27, 2015

First decision: August 31, 2015

Revised: October 14, 2015

Accepted: November 13, 2015

Article in press: November 13, 2015

Published online: January 21, 2016

Abstract

Inflammatory bowel disease (IBD) development is affected by complex interactions between environmental factors, changes in intestinal flora, various predisposing genetic properties and changes in the immune system. Dietary factors seem to play an underestimated role in the etiopathogenesis and course of the disease. However, research about food and IBD is conflicting. An excessive consumption of sugar, animal fat and linoleic acid is considered a risk factor for IBD development, whereas a high fiber diet and citrus fruit consumption may play a protective role. Also, appropriate nutrition in particular periods of the disease may facilitate achieving or prolonging remissions and most of all, improve the quality of life for patients. During disease exacerbation, a low fiber diet is recommended for most patients. In the remission time, an excessive consumption of alcohol and sulfur products may have a negative effect on the disease course. Attempts are also made at employing diets composed in detail in order to supplement IBD therapy. A diet with a modified carbohydrate composition, a semi-vegetarian diet and a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols are under investigation. Due to chronic inflammation as well as side effects of chronically used medications, patients with IBD are also at increased risk of nutritional factor deficiencies, including iron, calcium, vitamin D, vitamin B12, folic acid, zinc, magnesium and vitamin A. It should also be remembered that there is no single common diet suitable for all IBD patients; each of them is unique and dietary recommendations must be individually developed for each patient, depending on the course of the disease, past surgical procedures and type of pharmacotherapy.

Key words: Crohn's disease; Diet; Nutrition; Supplementation; Ulcerative colitis

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The role of dietary factors in inflammatory bowel diseases (IBD) development seems to be underestimated although approximately 70% of IBD patients are known to employ elimination diets while in remission, affecting their social and family life. We would like to draw attention to this growing problem. The objective of our paper is to present up to date information regarding the effect of diet on IBD morbidity and course, together with the effect of IBD on the nutritional status of patients.

Owczarek D, Rodacki T, Domagała-Rodacka R, Cibor D, Mach T. Diet and nutritional factors in inflammatory bowel diseases. *World J Gastroenterol* 2016; 22(3): 895-905 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i3/895.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i3.895>

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are types of inflammatory bowel diseases (IBD). IBD constitutes chronic conditions, the etiology of which is not yet fully understood, and their course is characterized by periods of exacerbation and remission^[1-3]. In spite of their similar properties, UC and CD differ in their risk factors and genetic predispositions, and in their clinical, endoscopic and histological images^[2]. In UC, the inflammatory process solely involves the mucosa and extends by continuity, starting from the rectum. A characteristic symptom of UC is bloody diarrhea that may be accompanied by abdominal pain or fever^[2]. Moreover, patients in whom the inflammatory process is seen in the rectum only may develop constipation during the exacerbation periods of the disease. In CD, the inflammatory process involves the entire wall of the gastrointestinal tract and it is propagated segmentally, not by continuity, from the oral cavity to the rectum^[4]. Characteristic symptoms of CD are abdominal pain, fever, loss of body mass, anemia and diarrhea^[5].

While both conditions affect the gastrointestinal system, the role of diet in their course is often underestimated. Specifically, a literature analysis of the importance of environmental factors in the etiopathogenesis of IBD concluded that nutrition is an undervalued factor affecting IBD development.

During IBD exacerbation periods, recommending a low fiber diet is unquestionable^[6]. However, recommendations addressing the nutrition of patients in IBD remission remain controversial. As many as 70% of IBD patients are known to employ elimination diets during remission to avoid exacerbation of the disease, which affects both their social and family life^[7].

Such a high percentage of IBD patients employing dietary restrictions during remission has not been confirmed by the recommendations formulated by various gastroenterology organizations^[8-11]. In their recommendations for CD patients, the National Clinical Guideline Center advise a diversified and well balanced diet, without addressing a detailed composition^[11].

Patients with IBD should follow a diet that supplies an appropriate amount of energy, iron, calcium, zinc, folic acid and vitamins D and B12^[12]. Vitamin D deficiency is of particular importance as it may exacerbate the course of IBD and is additionally associated with an increased morbidity rate^[13,14].

Studies have also investigated diets of different compositions aimed to supplement therapy during periods of exacerbation, such as a modified carbohydrate diet (SCD) or a low fermentable oligo-saccharides, disaccharides, monosaccharides and polyols diet (FODMAP)^[15,16].

Additional supplementation with probiotics or unsaturated omega-3 fatty acids has been also assessed with respect to its effect on shortening exacerbation periods or prolonging remission duration^[17,18].

Numerous studies have attempted to demonstrate an association between IBD occurrence and dietary excess or deficiency of given foods^[4]. Dietary factors that may increase the risk of developing UC and CD include a high consumption of saturated fat and monosaccharides and a low consumption of fiber^[5,19,20].

The objective of this paper is to present the effects of diet on IBD course and morbidity, as well as to explore the effect of IBD on the nutritional status of patients. The presented results may be helpful in planning a diet for IBD patients.

ENVIRONMENTAL FACTORS AND INCIDENCE OF IBD

The incidence of IBD depends on numerous factors that are not fully understood. IBD development is affected by complex interactions between environmental factors, changes in intestinal flora, various predisposing genetic properties and changes in the immune system^[2,4].

The contribution of environmental factors is supported by an increased incidence of IBD in developed countries and urban populations, as opposed to developing countries and rural populations^[2]. In addition, some authors have drawn attention to an increased IBD incidence in countries with previously lower morbidity rates, such as countries in Asia. The investigators associate this effect with changes in the lifestyles of such populations.

Moreover, the effect of tobacco smoking on IBD development is well documented^[1,4,21]. Active smoking is an environmental factor that affects IBD incidence in two ways. It may exert a protective effect against

UC, while it increases the risk of CD development^[22,23]. However, in their meta-analysis, Jones *et al.*^[24] did not observe a correlation between passive smoking in childhood and IBD incidence.

Interesting reports address the importance of breastfeeding in IBD development. According to the meta-analysis performed by Klement *et al.*^[25], breastfeeding may be a protective factor in IBD morbidity. The authors suggest the necessity of performing further studies in order to confirm this hypothesis. Nevertheless, encouraging breastfeeding, especially in families affected by IBD, is warranted.

A literature analysis assessing the role of environmental factors in the etiopathogenesis of IBD highlights that diet is an underestimated factor affecting its development.

NUTRITIONAL FACTORS IN THE ETIOLOGY OF IBD

Many attempts have been made at associating the incidence of IBD with dietary excess or deficit of various foods^[4]. Indeed, a high intake of saturated fats and monosaccharides and a low intake of fiber are linked with increased risk of CD development^[19].

Monosaccharides and sweets

Numerous studies have emphasized the effect of an excessive consumption of dietary monosaccharides on IBD development. In retrospective studies, patients with CD showed an increased consumption of monosaccharides prior to feeling ill^[5,26]. Russel *et al.*^[27] emphasized the effect of consuming cola-type drinks and chocolate on increasing IBD incidence. Their observations were confirmed by Sakamoto *et al.*^[20], who demonstrated a negative effect of sweets and artificial sweeteners on the risk of developing both UC and CD. However, in 2014, Chan *et al.*^[28] presented results of a large prospective study of over 400000 men and women that demonstrated no association between total intake of carbohydrates, sugar or starch and incidence of UC or CD.

It should be stressed that lactose consumption does not increase the risk of IBD^[26].

Proteins and fats

According to Reif *et al.*^[26], an increased consumption of animal protein may result in a low degree of increased risk of IBD development. The same authors also demonstrated that a high fat diet, particularly one rich in cholesterol and animal fats, may increase IBD incidence^[26]. In their study, Ananthakrishnan *et al.*^[29] confirmed the effect of an increased consumption of trans fatty acids on the risk of UC development. The effect of consumption of linoleic acid, a polyunsaturated omega-6 fatty acid, on the risk of UC development has been also demonstrated. This fatty acid is a precursor of arachidonic acid (AA), the metabolites

of which exhibit pro-inflammatory properties^[30]. AA consumption may also increase UC risk, while an increased supply of oleic acid, a monounsaturated fatty acid, is a preventive factor^[31]. Based on a study of 25639 participants that completed a 7 d food diary, John *et al.*^[32] demonstrated a protective effect of unsaturated omega-3 fatty acid consumption on UC incidence; specifically, dietary intake of docosahexaenoic acid exerted beneficial effects. These observations have since been confirmed in publications by other authors^[29]. Based on studies carried out in Japan, Sakamoto *et al.*^[20] indicated a negative effect of total consumption of fats and unsaturated fatty acids on the risk of IBD development.

Fiber

Fiber consumption exerts a protective effect on IBD development as a high fiber diet decreases the risk of developing IBD^[26]. According to Ananthakrishnan *et al.*^[33], a diet with a fiber content of 24.3 g/d may decrease the risk of CD development by 40%. A particularly positive effect was noted with fiber originating from fruit sources. However, the authors did not observe any protective effect against UC development. In a study of 130 individuals under 30 years of age, Amre *et al.*^[34] confirmed the role of dietary fiber consumption on the prevention of CD.

Vitamins and minerals

Vitamin D deficiency is a common phenomenon in patients with IBD. As such, some authors regard this deficiency as a dietary factor that may increase the risk of IBD development^[13]. Reif *et al.*^[26] pointed to the protective effect of diets rich in fluids, magnesium and vitamin C on IBD risk; on the other hand, retinol-rich products may facilitate IBD development. It should be emphasized that fruit consumption, in view of the fiber and vitamin C content, may constitute a separate nutritional factor that decreases the risk of developing IBD^[26,33,34]. Fruit juices may also be recommended due to their anti-inflammatory and anti-oxidative activity^[35]. Russel *et al.*^[27] focused particularly on the beneficial effect of consuming citrus fruits.

Alcohol

Some studies have demonstrated a protective effect of alcohol consumption with respect to UC development. Nevertheless, this effect is negated when drinking alcohol is combined with cigarette smoking^[36]. No significant differences were observed in CD development between individuals consuming alcohol at least four times a week and teetotalers^[37].

DIET DURING PERIODS OF DISEASE EXACERBATION

Recommendations for low fiber intake are unquestionable in patients with exacerbated IBD,

diarrhea or abdominal pain^[6]. However, this does not apply to patients with UC and rectal involvement only who may develop constipation. Such patients are advised to be on a fiber rich diet, in keeping with the recommendations of the World Gastroenterology Organization^[6]. According to the recommendations of the European Crohn's and Colitis Organization (ECCO), pediatric patients with exacerbated UC of mild to moderate intensity are advised to be on a normal diet^[10]. Patients with inadequate nutritional supply may be recommended to remain on exclusive enteral nutrition (EEN) with liquid preparations containing all the necessary nutrients^[10,38]. In keeping with the ECCO recommendations, in case of UC, EEN does not play a therapeutic role^[10]. On the other hand, EEN may result in CD remission. In a review of studies addressing EEN employment in children, its effectiveness in achieving remission was equal to that of glucocorticosteroid therapy^[39]. In adult patients, the results were somewhat less encouraging. The meta-analysis performed by Zachos *et al.*^[40] indicated the advantage of glucocorticosteroids over EEN in achieving CD remission. The authors did not demonstrate any differences between the effectiveness of elemental and polymeric diets^[40]. EEN was also shown to accelerate gastrointestinal mucosal healing in pediatric patients with CD^[41]. It is important to gradually introduce a normal diet after 8 wk of EEN feeding. The introduction of a normal diet should span approximately 7-10 d, with one meal introduced every 3-4 d^[38].

DIET DURING REMISSION PERIODS

The nutritional model presented above for patients with exacerbated IBD remains undisputed. However, recommendations addressing the diet of patients in remission are not unambiguous. According to Zallot *et al.*^[7], as many as 2/3 of IBD patients employ an elimination diet to avoid disease exacerbation. Such behavior affects their social life by limiting the occasions when meals are eaten outside the home or in eating different meals to other household members. In spite of such phenomena, numerous official recommendations do not address the subject of nutrition of IBD patients. This is additionally complicated by the fact that investigations carried out by various authors present contradictory results. The next section of this report discusses recommendations presented by various scientific societies as well as the results of studies that may be helpful in planning a diet for IBD patients.

Recommendations of scientific associations

The body of recommendations of the American College of Gastroenterology addressing UC do not include dietary recommendations^[8] and only address nutrition during CD exacerbation periods^[9]. For the management of pediatric UC patients, ECCO does not

advise the use of any special diets and supplements due to their lack of effect on the disease course^[10]. However, the recommendations for nutritional management of CD from the National Clinical Guideline Center advise patients in remission to be on a diversified and well-balanced diet, but do not address a detailed composition^[11].

Results of other publications

In a review, Akobeng *et al.*^[42] pointed to the role of enteral nutrition in prolonging periods of remission in patients with CD. Beneficial effects were achieved by providing 35%-50% of calorie requirements by means of enteral nutrition, compared to a normal diet. The authors suggested the necessity of conducting further larger studies to confirm this hypothesis^[42]. Other authors pointed to a negative effect of sulfur products on UC course^[43]. Sulfur and its compounds exert a negative effect on colonocytes by increasing the intestinal concentration of hydrogen sulfide. Sources of dietary sulfur include high protein products due to the presence of sulfur-containing amino acids and include red meat, cheese, eggs and nuts. Foods rich in inorganic sulfur compounds include the cruciferous vegetables and preserved products. According to Jowett *et al.*^[43], restricting dietary red meat intake (for reasons described above) may prolong periods of remission. In the same report, the authors did not find a negative effect of dairy product consumption on the course of the disease or a protective effect of a high fiber diet^[43]. Contradictory results were obtained by Fernández-Bañares *et al.*^[44]. In the course of their study, they administered 10 g of psyllium seeds twice a day to UC patients and compared the effectiveness of such treatment with patients receiving 500 mg of mesalazine administered three times a day and with a third group of patients receiving fiber and mesalazine. After 12 mo, recurrent disease was noted in 40% of patients in the fiber group, 35% in the mesalazine group, and 30% in the combined group. Based on these results, the authors concluded that a high fiber diet may prevent recurrent UC in a manner comparable to mesalazine^[44]. The above conclusion was confirmed by Hallert *et al.*^[45] who also pointed to a beneficial effect of psyllium seed husks on amelioration of UC symptoms in patients in remission. Based on a review, Wedlake *et al.*^[46] indicated a mildly beneficial effect of fiber on the course of UC. The results obtained for CD patients did not indicate a positive role for a high fiber diet in improving clinical status^[46]. On the other hand, other studies demonstrated a beneficial effect of a high fiber diet on gastrointestinal function in CD patients, which was based on the Inflammatory Bowel Disease Questionnaire and the Harvey Bradshaw Index^[47]. This nutritional model did not result in adverse effects; however, it did not affect inflammatory markers (no differences were noted between C-reactive protein levels in the study

and control groups), which may suggest its limited importance in the course of CD^[47].

Germinated barley foodstuff (GBF) is a source of fiber and glutamine-rich protein. GBF is a prebiotic product that increases butyrate production by intestinal bacteria. These compounds may affect the repair and restoration of function of colonocytes^[48]. In their limited study, Bamba *et al.*^[49] administered 20-30 g of GBF to patients with mild or moderate UC exacerbation. After 4 wk of therapy, the patients demonstrated clinical and endoscopic improvements, thus indicating that GBF may play an important role in IBD therapy^[49]. Hanai *et al.*^[50] confirmed these results by demonstrating a beneficial effect of supplementing a standard therapy with 20 g of GBF. Patients receiving prebiotic supplementation demonstrated an improvement of clinical status as well as prolonged remission. The above results require confirmation in a large scale study.

Some studies pointed to a negative effect of alcohol consumption on the course of IBD. According to Swanson *et al.*^[51], in patients with non-active UC and CD, alcohol resulted in exacerbation of gastrointestinal symptoms. Moreover, Jowett *et al.*^[43] indicated that alcohol consumption increased the risk of disease exacerbation in patients with UC.

Attempts have also been made at implementing detailed diets to supplement IBD therapy. Olendzki *et al.*^[52] used a specially developed menu low in refined sugars, rich in prebiotic and probiotic products and characterized by an appropriate ratio of fatty acids. Of 40 patients included in the study, 13 abandoned the diet early and 24 demonstrated a very good or good response to the diet based on self-assessment of disease symptoms and adherence to the principles of the diet. Three patients showed an ambiguous or negative response. Of all the participants, the case histories of 11 patients for whom complete data were available were analyzed. In these patients, when the diet was employed for 4 wk or longer, IBD symptom reduction was noted based on the Harvey Bradshaw Index and the Modified Truelove and Witts Severity Index. All patients were able to discontinue at least one of their previously used IBD medications. This example indicates the possibility of deriving additional benefits from supplementing pharmacotherapy by an appropriately composed diet^[52]. Moreover, Cohen *et al.*^[15], prescribed pediatric patients with a SCD diet. The patients restricted refined sugar and complex carbohydrate consumption and those that followed the diet for 12-52 wk showed an improved clinical status. A similar problem was addressed by Suskind *et al.*^[53] when they analyzed the effect of the SCD diet on CD course in pediatric patients for 5-30 mo. Improvements in clinical status were seen in the patients following the SCD diet^[53]. The results of these two studies require confirmation of the effectiveness and safety of the SCD

diet in a larger group of patients.

Chiba *et al.*^[54] investigated the effect of a semi-vegetarian diet (SVD) on maintaining CD remission. Sixteen patients continued the recommended diet after discharge from hospital. The percentage of remission achieved in the study group was 100% after one year of starting the SVD and 92% after two years. Based on these observations, the authors recognized the SVD as a highly effective diet in maintaining CD remission^[54].

Another type of diet employed for IBD therapy is the FODMAP diet, which is low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols^[16]. This nutritional model is based on a theory suggesting that poorly absorbed carbohydrates become a medium for bacteria and may cause excessive growth of intestinal flora, and was originally recommended for use in irritable bowel syndrome patients. Geary *et al.*^[16] assessed the effect of the diet on the course of IBD; the study included 52 patients with CD and 20 individuals with UC. Approximately 50% of patients noted a decrease in abdominal pain, flatulence and diarrhea. Thus, the FODMAP diet is recognized to be helpful for patients with IBD with concomitant functional intestinal symptoms^[16].

In these studies, the investigators evaluated the effect of various nutrients and detailed diets on the course of IBD. Despite the lack of tangible dietary recommendations for patients suffering from UC and CD, it is important to take into account the possibility of developing deficiencies associated with gastrointestinal status, administered medications, past surgical procedures or limited appetite^[12]. While planning a diet, it is necessary to pay particular attention to key nutrients.

KEY NUTRIENTS IN THE DIET OF IBD PATIENTS

When recommending a given diet to an IBD patient, emphasis should be placed on adequate caloric supply as well as the content of iron, calcium, vitamins D, B₁₂ and A, folic acid and zinc^[12].

Energy

Malnutrition may affect 20%-85% of CD patients^[55]. Therefore it is important that their diet be appropriately planned. Of significance is an appropriate supply of energy, vitamins and minerals as deficiencies in these may develop during the course of the disease. Loss of appetite may hinder the consumption of an adequate amount of food. For this reason, the European Society for Clinical Nutrition and Metabolism recommends an intake of up to 600 kcal/d in the form of oral nutritional supplements^[55] since the consequences of nutritional deficiencies may include anemia, osteomalacia, osteoporosis and problems

with mesopic vision^[55].

Iron

Anemia often coexists with IBD, affecting 21%-88% of IBD patients^[4,55-57]. The principal cause of anemia is iron deficiency (approximately 57%) but it may also be caused by a chronic inflammatory state or be due to vitamin B₁₂ deficiency^[56]. According to the World Health Organization recommendations, excessively low hemoglobin (Hb) concentrations occur when Hb levels drop below 11-13 g/dL (depending on sex and age group). Determining the changes in ferritin levels allows for differentiating between various types of anemia. Decreased concentrations of the protein are observed in anemia caused by iron deficiency, while in patients with inflammatory states, ferritin concentrations are elevated. Due to a poor tolerance of oral iron preparations and the risk of exacerbation of the gastrointestinal inflammatory state, intravenous preparations are administered for anemia treatment in patients with IBD^[56,57].

Calcium

Patients with IBD are at risk of developing osteoporosis. This is related to malnutrition which is common in this group and to problems with absorption of nutrients^[55], also due to the administration of glucocorticosteroids. For the above reasons, it is important that an adequate dietary calcium supply of 1000-1500 mg/d is attained. Patients with IBD often give up milk and dairy products for fear of lactose consumption. It should be emphasized that intolerance of the disaccharide is not more common in this patient population compared to healthy subjects and its occurrence is affected by age and ethnic factors rather than by IBD alone^[12,58-60]. In cases of lactose intolerance or problems with dietary calcium supply, calcium supplementation should be considered.

Vitamin D

Vitamin D is a fat-soluble vitamin whose role in the development of IBD has long been underestimated; its levels are associated with IBD morbidity and course. Vitamin D deficiency facilitates the development of CD and UC and may worsen their course^[13,14]. Jørgensen *et al.*^[14] examined patients with CD and demonstrated an inverse relationship between serum vitamin D levels and disease activity. Hlavaty *et al.*^[61] carried out a study among patients with IBD using a questionnaire evaluating "health-related quality of life". They demonstrated a decrease in the evaluated parameters in the winter/spring period, which correlated with a decreased serum vitamin D concentration. CD patients may develop vitamin D deficiency due to malabsorption^[55]. Such a deficiency, as demonstrated by Abraham *et al.*^[62], facilitates the loss of bone mineral density. Vitamin D supplementation may be introduced; studies point to a positive effect of such

an intervention exerted on the disease course^[63]. In their study, Jørgensen *et al.*^[63] administered vitamin D at a dose of 1200 IU to CD patients. After three months of treatment, recurrent disease was noted in 13% (6/46) of the study group patients as opposed to 29% (14/48) of the subjects in the control group. The authors stressed the necessity of confirming their results in a larger study. In turn, Pappa *et al.*^[64] administered different doses of vitamin D to two groups of pediatric patients aged 8-18 years. Group A received 400 IU daily, all year long and, depending on the season of the year, Group B received 1000 IU (summer/autumn) or 2000 IU (winter/spring). The doses were selected in a way that allowed the target serum vitamin concentration value (> 32 ng/mL) to be achieved in only 3% of patients in both groups. The authors observed lower C-reactive protein and interleukin-6 levels in the patients receiving higher doses of the vitamin. These results may indicate a beneficial effect of vitamin D supplementation on IBD-associated inflammatory processes; however, these observations require confirmation. Dadaei *et al.*^[65] administered vitamin D at a dose of 50000 IU per week for 12 wk, resulting in increased serum levels and decreased levels of tumor necrosis factor (TNF- α). However, the decrease in TNF- α levels did not reach statistical significance.

Other studies have observed an increased risk of *Clostridium difficile* infections and development of cancers (especially colon cancer) in IBD patients with decreased vitamin D levels^[66,67]. In view of the growing number of publications on the role of vitamin D in IBD and continued doubts surrounding the selection of an appropriate dose, further studies on vitamin D supplementation are warranted.

B vitamins

B vitamin deficiencies in patients with CD are also frequent (B₁₂: 28%-48% and folic acid: 4.3%-54%)^[19,55]. Problems with cyanocobalamin absorption may occur after resection of the distal part of the intestine or with particularly intensified disease involving the distal gastrointestinal tract. The risk of folic acid deficiency increases in patients treated with sulphasalazine^[19]. Deficiencies of B vitamins may facilitate the development of macrocytic anemia and hyperhomocysteinemia. For this reason, the level of cyanocobalamin should be monitored and vitamin B₁₂ preparations should be administered parenterally if needed in order to treat the deficiency. Patients who are at risk for folate deficiency should supplement with folic acid when necessary^[19,55].

Deficiencies of other vitamins and minerals

Patients with CD may also present with zinc (70% of males) and magnesium deficiencies^[11,19]. Moreover, vitamin A deficiency may occur during phases of active disease^[19]. A well planned diet should include foods

Table 1 Foods and particular nutrients affecting inflammatory bowel diseases incidence

Protective factors	Nutrients increasing IBD morbidity
Breastfeeding	Cholesterol
Fiber	Animal fats
Vitamin D	Linoleic and arachidonic acids
Appropriate fluid supply	Monosaccharides (ambiguous study results)
Vitamin C	
Fruits (especially citrus fruits)	
Magnesium	

IBD: Inflammatory bowel diseases.

Table 2 Diet to be employed during disease exacerbation periods

Beneficial effect	Negative effect
Solely enteral feeding (EEN) (in case of Crohn's disease, especially in pediatric patients)	Fiber (exception - patients with ulcerative proctitis with concomitant constipation)

that are rich in these components, such as β -carotene-containing vegetables (carrots, red peppers), nuts, groats and wholegrain products^[68].

ADDITIONAL SUPPLEMENTATION IN IBD

Numerous reports have investigated employing additional supplementation with components that may shorten the duration of exacerbated disease periods or that prolong phases of remission. Particular attention has been given to preparations containing probiotics and unsaturated omega-3 fatty acids.

Probiotics

IBD morbidity may be related to gastrointestinal bacterial flora abnormalities and to an abnormal immune response to physiological flora^[4,69]. For these reasons, investigations were carried out to determine the effects of probiotic supplementation on the course of UC and CD. Specifically, the effects of various probiotics on achieving and maintaining IBD remission were studied. The results differed depending on the bacterial strain and type of disease and contradictory results were obtained for some probiotics. In their review paper, Jonkers *et al.*^[17] demonstrated a lack of sufficient evidence in support of the beneficial effects of probiotic supplementation in CD. At the same time, the authors emphasized promising results of studies on the *Escherichia coli* strain Nissle 1917 for the prevention of disease exacerbation and on a multi-strain product containing *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus bulgaricus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis* and

Streptococcus thermophilus (VSL#3) during active and inactive phases of UC^[17]. Additionally, a meta-analysis by Shen *et al.*^[70] and a study by Miele *et al.*^[71] indicated a beneficial effect of supplementation with VSL#3 on achieving and maintaining UC remission. Other probiotic strains that fostered the interest of investigators include *Lactobacillus* GG (LGG) and *Saccharomyces boulardii* (SB)^[72]. A study administered a dose of 1 g/d of *Saccharomyces boulardii* to patients in CD remission; however, no beneficial effects were found on the course of CD compared with placebo. Differences in the response to supplementation were shown solely in non-smoking patients; an effect that requires future investigation^[72]. Guslandi *et al.*^[73,74] performed two small scale studies (32 and 25 individuals) that found a beneficial effect of SB supplementation in maintaining remission of CD and UC. In both studies, the probiotic was given in addition to mesalazine therapy. Gupta *et al.*^[75] administered LGG to four children with CD at a dose of 10^{10} colony forming units, twice a day, for six months. Based on the decrease in the initial values of the Pediatric Crohn's Disease Activity Index, the investigators found a decrease in disease activity in their patients. Additionally, a reduction in the dose of glucocorticosteroids given was achieved in three participants. On the other hand, a study by Bousvaros *et al.*^[76] employing the same strain in a group of 75 children with CD found no effect of supplementation on prolonging remission. Similar results indicating lack of effectiveness of LGG in CD were obtained by Prantera *et al.*^[77].

To date, despite solid theoretical foundations, no beneficial effects of probiotic supplementation on the course of IBD have been unambiguously demonstrated. The most promising results have been achieved when probiotic preparations containing the given bacterial strains were employed in UC^[17,69-71].

Unsaturated omega-3 fatty acids

Other nutritional components that may affect the course of IBD are polyunsaturated omega-3 fatty acids (n-3 PUFA). These fatty acids have been studied for their anti-inflammatory activity^[18]. In a review, Farrukh and Mayberry described a slight beneficial effect of PUFA supplementation during active disease. The results of various studies have pointed to a faster achievement of remission and the possibility of reducing the dose of glucocorticosteroids with n-3 PUFA supplementation. However, the majority of studies have not confirmed the effects of PUFA on maintaining IBD remission. Less convincing results were obtained of the effects of n-3 PUFA on CD. Nevertheless, supplementation did achieve positive results in some studies. Further trials are warranted to determine the beneficial effects of omega-3 fatty acids on the disease course of IBD^[18,55].

Table 3 Diet to be employed during remissions

Beneficial effect	Negative effect
Prolonged partial enteral nutrition	Sulfur products (dietary sulfur sources - red meat, cheese, eggs, nuts)
Fiber	Alcohol
Psyllium seeds (especially in UC, a poorer effect in CD)	
Germinated barley foodstuff (GBF)	
Special types of diet	
Anti-inflammatory diet - Olendzki <i>et al</i> ^[52]	
Semi-vegetarian diet (SVD)	
Diet with specialty modified carbohydrate composition (SCD)	
Diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP)	

UC: Ulcerative colitis; CD: Crohn's disease.

Table 4 Key nutrients and dietary supplements in inflammatory bowel diseases patients

Nutrients that may be deficient in IBD	Dietary supplements aiding in IBD therapy
Energy	Probiotics
Iron	<i>Escherichia coli</i> Nissle 1917 (in particular in UC)
Calcium	VSL#3 (in particular in UC)
Vitamin D	<i>Saccharomyces boulardii</i> (ambiguous study results)
Vitamin B ₁₂ (in particular in patients after resection of the distal part of the intestine or with particularly intensified disease involving this part of the gastrointestinal tract)	<i>Lactobacillus</i> LGG (ambiguous study results)
Folic acid (in particular in patients treated with sulphasalazine)	Unsaturated omega-3 fatty acids (a small effect in UC, a poorer effect in CD)
Zinc (in particular in CD)	
Magnesium (in particular in CD)	
Vitamin A (in particular in active CD)	

IBD: Inflammatory bowel diseases; UC: Ulcerative colitis; CD: Crohn's disease.

CONCLUSION

Dietary factors play an underestimated role in the etiopathogenesis and course of IBD. The effects of numerous nutritional factors have been well documented (Tables 1, 2, 3 and 4).

Employing an appropriate diet may decrease the risk of developing IBD, which may be of special importance for individuals affected by such diseases. In particular, appropriate nutrition during periods of the disease may facilitate achieving or prolonging stages of remission and, importantly, improve comfort and quality of life.

However, there is no single diet suitable for all IBD patients; unique dietary recommendations must be

developed for each patient, depending on the course of the disease, past surgical procedures and type of pharmacotherapy used.

For the above reasons, dietary recommendations should be treated as supplementation of pharmacotherapy in IBD.

REFERENCES

- 1 **Malaty HM**, Hou JK, Thirumurthi S. Epidemiology of inflammatory bowel disease among an indigent multi-ethnic population in the United States. *Clin Exp Gastroenterol* 2010; **3**: 165-170 [PMID: 21694862 DOI: 10.2147/CEG.S14586]
- 2 **Ordás I**, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet* 2012; **380**: 1606-1619 [PMID: 22914296 DOI: 10.1016/S0140-6736(12)60150-0]
- 3 **Jakubowski A**, Zagórowicz E, Kraszewska E, Bartnik W. Rising hospitalization rates for inflammatory bowel disease in Poland. *Pol Arch Med Wewn* 2014; **124**: 180-190 [PMID: 24727650]
- 4 **Baumgart DC**, Sandborn WJ. Crohn's disease. *Lancet* 2012; **380**: 1590-1605 [PMID: 22914295 DOI: 10.1016/S0140-6736(12)60026-9]
- 5 **Riordan AM**, Ruxton CH, Hunter JO. A review of associations between Crohn's disease and consumption of sugars. *Eur J Clin Nutr* 1998; **52**: 229-238 [PMID: 9578334]
- 6 Inflammatory bowel disease: a global perspective. World Gastroenterology Organisation Global Guidelines. June 2009. Available from: URL: http://www.medscape.com/index/list_7515_2
- 7 **Zallot C**, Quilliot D, Chevaux JB, Peyrin-Biroulet C, Guéant-Rodriguez RM, Freling E, Collet-Fenetrier B, Williet N, Ziegler O, Bigard MA, Guéant JL, Peyrin-Biroulet L. Dietary beliefs and behavior among inflammatory bowel disease patients. *Inflamm Bowel Dis* 2013; **19**: 66-72 [PMID: 22467242 DOI: 10.1002/ibd.22965]
- 8 **Kornbluth A**, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; **105**: 501-523; quiz 524 [PMID: 20068560 DOI: 10.1038/ajg.2009.727]
- 9 **Lichtenstein GR**, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology. Management of Crohn's disease in adults. *Am J Gastroenterol* 2009; **104**: 465-483; quiz 464, 484 [PMID: 19174807 DOI: 10.1038/ajg.2008.168]
- 10 **Turner D**, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, Dias JA, Bronsky J, Braegger CP, Cucchiara S, de Ridder L, Fagerberg UL, Hussey S, Hugot JP, Kolacek S, Kolho KL, Lionetti P, Paeerregaard A, Potapov A, Rintala R, Serban DE, Staiano A, Sweeny B, Veerman G, Veres G, Wilson DC, Rummelle FM. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012; **55**: 340-361 [PMID: 22773060]
- 11 **National Institute for Health and Clinical Excellence: Guidance**. Crohn's disease: Management in adults, children and young people. National Clinical Guideline Centre: October, 2012
- 12 **Silva AFD**, Schieferdecker MEM, Amarante HMBDS. Food intake in patients with inflammatory bowel disease. *Arq Bras Cir Dig* 2011; **24**: 204-209
- 13 **Zhang YZ**, Li YY. Inflammatory bowel disease: pathogenesis. *World J Gastroenterol* 2014; **20**: 91-99 [PMID: 24415861 DOI: 10.3748/wjg.v20.i1.91]
- 14 **Jørgensen SP**, Hvas CL, Agnholt J, Christensen LA, Heickendorff L, Dahlerup JF. Active Crohn's disease is associated with low vitamin D levels. *J Crohns Colitis* 2013; **7**: e407-e413 [PMID: 23403039 DOI: 10.1016/j.crohns.2013.01.012]
- 15 **Cohen SA**, Gold BD, Oliva S, Lewis J, Stallworth A, Koch B, Eshee L, Mason D. Clinical and mucosal improvement with specific carbohydrate diet in pediatric Crohn disease. *J Pediatr*

- Gastroenterol Nutr* 2014; **59**: 516-521 [PMID: 24897165 DOI: 10.1097/MPG.0000000000000449]
- 16 **Gearry RB**, Irving PM, Barrett JS, Nathan DM, Shepherd SJ, Gibson PR. Reduction of dietary poorly absorbed short-chain carbohydrates (FODMAPs) improves abdominal symptoms in patients with inflammatory bowel disease—a pilot study. *J Crohns Colitis* 2009; **3**: 8-14 [PMID: 21172242 DOI: 10.1016/j.crohns.2008.09.004]
 - 17 **Jonkers D**, Penders J, Masclee A, Pierik M. Probiotics in the management of inflammatory bowel disease: a systematic review of intervention studies in adult patients. *Drugs* 2012; **72**: 803-823 [PMID: 22512365 DOI: 10.2165/11632710-000000000-00000]
 - 18 **Farrukh A**, Mayberry JF. Is there a role for fish oil in inflammatory bowel disease? *World J Clin Cases* 2014; **2**: 250-252 [PMID: 25032198 DOI: 10.12998/wjcc.v2.i7.250]
 - 19 **Basson A**. Nutrition management in the adult patient with Crohn's disease. *S Afr J Clin Nutr* 2012; **25**: 164-172
 - 20 **Sakamoto N**, Kono S, Wakai K, Fukuda Y, Satomi M, Shimoyama T, Inaba Y, Miyake Y, Sasaki S, Okamoto K, Kobashi G, Washio M, Yokoyama T, Date C, Tanaka H. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. *Inflamm Bowel Dis* 2005; **11**: 154-163 [PMID: 15677909]
 - 21 **Kanai T**, Matsuoka K, Naganuma M, Hayashi A, Hisamatsu T. Diet, microbiota, and inflammatory bowel disease: lessons from Japanese foods. *Korean J Intern Med* 2014; **29**: 409-415 [PMID: 25045286 DOI: 10.3904/kjim.2014.29.4.409]
 - 22 **Tuvlin JA**, Raza SS, Bracamonte S, Julian C, Hanauer SB, Nicolae DL, King AC, Cho JH. Smoking and inflammatory bowel disease: trends in familial and sporadic cohorts. *Inflamm Bowel Dis* 2007; **13**: 573-579 [PMID: 17345609]
 - 23 **Mahid SS**, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc* 2006; **81**: 1462-1471 [PMID: 17120402]
 - 24 **Jones DT**, Osterman MT, Bewtra M, Lewis JD. Passive smoking and inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol* 2008; **103**: 2382-2393 [PMID: 18844625 DOI: 10.1111/j.1572-024]
 - 25 **Klement E**, Cohen RV, Boxman J, Joseph A, Reif S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. *Am J Clin Nutr* 2004; **80**: 1342-1352 [PMID: 15531685]
 - 26 **Reif S**, Klein I, Lubin F, Farbstein M, Hallak A, Gilat T. Pre-illness dietary factors in inflammatory bowel disease. *Gut* 1997; **40**: 754-760 [PMID: 9245929]
 - 27 **Russel MG**, Engels LG, Muris JW, Limonard CB, Volovics A, Brummer RJ, Stockbrügger RW. Modern life' in the epidemiology of inflammatory bowel disease: a case-control study with special emphasis on nutritional factors. *Eur J Gastroenterol Hepatol* 1998; **10**: 243-249 [PMID: 9585029]
 - 28 **Chan SS**, Luben R, van Schaik F, Oldenburg B, Bueno-de-Mesquita HB, Hallmans G, Karling P, Lindgren S, Grip O, Key T, Crowe FL, Bergmann MM, Overvad K, Palli D, Masala G, Khaw KT, Racine A, Carbonnel F, Boutron-Ruault MC, Olsen A, Tjonneland A, Kaaks R, Tumino R, Trichopoulou A, Hart AR. Carbohydrate intake in the etiology of Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2014; **20**: 2013-2021 [PMID: 25265262 DOI: 10.1097/MIB.0000000000000168]
 - 29 **Ananthkrishnan AN**, Khalili H, Konijeti GG, Higuchi LM, de Silva P, Fuchs CS, Willett WC, Richter JM, Chan AT. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. *Gut* 2014; **63**: 776-784 [PMID: 23828881 DOI: 10.1136/gutjnl-2013-305304]
 - 30 **Tjonneland A**, Overvad K, Bergmann MM, Nagel G, Linseisen J, Hallmans G, Palmqvist R, Sjodin H, Hagglund G, Berglund G, Lindgren S, Grip O, Palli D, Day NE, Khaw KT, Bingham S, Riboli E, Kennedy H, Hart A. Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: a nested case-control study within a European prospective cohort study. *Gut* 2009; **58**: 1606-1611 [PMID: 19628674 DOI: 10.1136/gut.2008.169078]
 - 31 **de Silva PS**, Luben R, Shrestha SS, Khaw KT, Hart AR. Dietary arachidonic and oleic acid intake in ulcerative colitis etiology: a prospective cohort study using 7-day food diaries. *Eur J Gastroenterol Hepatol* 2014; **26**: 11-18 [PMID: 24216567 DOI: 10.1097/MEG.0b013e3283365c372]
 - 32 **John S**, Luben R, Shrestha SS, Welch A, Khaw KT, Hart AR. Dietary n-3 polyunsaturated fatty acids and the aetiology of ulcerative colitis: a UK prospective cohort study. *Eur J Gastroenterol Hepatol* 2010; **22**: 602-606 [PMID: 20216220 DOI: 10.1097/MEG.0b013e3283352d05]
 - 33 **Ananthkrishnan AN**, Khalili H, Konijeti GG, Higuchi LM, de Silva P, Korzenik JR, Fuchs CS, Willett WC, Richter JM, Chan AT. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. *Gastroenterology* 2013; **145**: 970-977 [PMID: 23912083 DOI: 10.1053/j.gastro.2013.07.050]
 - 34 **Amre DK**, D'Souza S, Morgan K, Seidman G, Lambrette P, Grimard G, Israel D, Mack D, Ghadirian P, Deslandres C, Chotard V, Budai B, Law L, Levy E, Seidman EG. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. *Am J Gastroenterol* 2007; **102**: 2016-2025 [PMID: 17617201]
 - 35 **Rossi T**, Gallo C, Bassani B, Canali S, Albini A, Bruno A. Drink your prevention: beverages with cancer preventive phytochemicals. *Pol Arch Med Wewn* 2014; **124**: 713-722 [PMID: 25490889]
 - 36 **El-Tawil AM**. Epidemiology and inflammatory bowel diseases. *World J Gastroenterol* 2013; **19**: 1505-1507 [PMID: 23539486 DOI: 10.3748/wjg.v19.i10.1505]
 - 37 **Han DY**, Fraser AG, Dryland P, Ferguson LR. Environmental factors in the development of chronic inflammation: a case-control study on risk factors for Crohn's disease within New Zealand. *Mutat Res* 2010; **690**: 116-122 [PMID: 19751746 DOI: 10.1016/j.mrfmmm.2009.09.002]
 - 38 **Bishop J**, Lemberg DA, Day A. Managing inflammatory bowel disease in adolescent patients. *Adolesc Health Med Ther* 2014; **5**: 1-13 [PMID: 24729736 DOI: 10.2147/AHMT.S37956]
 - 39 **Dziechciarz P**, Horvath A, Shamir R, Szajewska H. Meta-analysis: enteral nutrition in active Crohn's disease in children. *Aliment Pharmacol Ther* 2007; **26**: 795-806 [PMID: 17767463]
 - 40 **Zachos M**, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007; **(1)**: CD000542 [PMID: 17253452]
 - 41 **Borrelli O**, Cordischi L, Cirulli M, Paganelli M, Labalestra V, Uccini S, Russo PM, Cucchiara S. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol* 2006; **4**: 744-753 [PMID: 16682258]
 - 42 **Akobeng AK**, Thomas AG. Enteral nutrition for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007; **(3)**: CD005984 [PMID: 17636816]
 - 43 **Jowett SL**, Seal CJ, Pearce MS, Phillips E, Gregory W, Barton JR, Welfare MR. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. *Gut* 2004; **53**: 1479-1484 [PMID: 15361498]
 - 44 **Fernández-Bañares F**, Hinojosa J, Sánchez-Lombraña JL, Navarro E, Martínez-Salmerón JF, García-Pugés A, González-Huix F, Riera J, González-Lara V, Domínguez-Abascal F, Giné JJ, Moles J, Gomollón F, Gassull MA. Randomized clinical trial of *Plantago ovata* seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. Spanish Group for the Study of Crohn's Disease and Ulcerative Colitis (GETECCU). *Am J Gastroenterol* 1999; **94**: 427-433 [PMID: 10022641]
 - 45 **Hallert C**, Kaldma M, Petersson BG. Ispaghula husk may relieve gastrointestinal symptoms in ulcerative colitis in remission. *Scand J Gastroenterol* 1991; **26**: 747-750 [PMID: 1654592]
 - 46 **Wedlake L**, Slack N, Andreyev HJ, Whelan K. Fiber in the treatment and maintenance of inflammatory bowel disease: a systematic review of randomized controlled trials. *Inflamm Bowel Dis* 2014; **20**: 576-586 [PMID: 24445775]

- 47 **Brotherton CS**, Taylor AG, Bourguignon C, Anderson JG. A high-fiber diet may improve bowel function and health-related quality of life in patients with Crohn disease. *Gastroenterol Nurs* 2014; **37**: 206-216 [PMID: 24871666 DOI: 10.1097/SGA.0000000000000047]
- 48 **Kanauchi O**, Iwanaga T, Andoh A, Araki Y, Nakamura T, Mitsuyama K, Suzuki A, Hibi T, Bamba T. Dietary fiber fraction of germinated barley foodstuff attenuated mucosal damage and diarrhea, and accelerated the repair of the colonic mucosa in an experimental colitis. *J Gastroenterol Hepatol* 2001; **16**: 160-168 [PMID: 11207896]
- 49 **Bamba T**, Kanauchi O, Andoh A, Fujiyama Y. A new prebiotic from germinated barley for nutraceutical treatment of ulcerative colitis. *J Gastroenterol Hepatol* 2002; **17**: 818-824 [PMID: 12164955]
- 50 **Hanai H**, Kanauchi O, Mitsuyama K, Andoh A, Takeuchi K, Takayuki I, Araki Y, Fujiyama Y, Toyonaga A, Sata M, Kojima A, Fukuda M, Bamba T. Germinated barley foodstuff prolongs remission in patients with ulcerative colitis. *Int J Mol Med* 2004; **13**: 643-647 [PMID: 15067363]
- 51 **Swanson GR**, Sedghi S, Farhadi A, Keshavarzian A. Pattern of alcohol consumption and its effect on gastrointestinal symptoms in inflammatory bowel disease. *Alcohol* 2010; **44**: 223-228 [PMID: 20682190 DOI: 10.1016/j.alcohol.2009.10.019]
- 52 **Oleńdzki BC**, Silverstein TD, Persuitt GM, Ma Y, Baldwin KR, Cave D. An anti-inflammatory diet as treatment for inflammatory bowel disease: a case series report. *Nutr J* 2014; **13**: 5 [PMID: 24428901 DOI: 10.1186/1475-2891-13-5]
- 53 **Suskind DL**, Wahbeh G, Gregory N, Vendettuoli H, Christie D. Nutritional therapy in pediatric Crohn disease: the specific carbohydrate diet. *J Pediatr Gastroenterol Nutr* 2014; **58**: 87-91 [PMID: 24048168 DOI: 10.1097/MPG.000000000000103]
- 54 **Chiba M**, Abe T, Tsuda H, Sugawara T, Tsuda S, Tozawa H, Fujiwara K, Imai H. Lifestyle-related disease in Crohn's disease: relapse prevention by a semi-vegetarian diet. *World J Gastroenterol* 2010; **16**: 2484-2495 [PMID: 20503448 DOI: 10.3748/wjg.v16.i20.2484]
- 55 **Donnellan CF**, Yann LH, Lal S. Nutritional management of Crohn's disease. *Therap Adv Gastroenterol* 2013; **6**: 231-242 [PMID: 23634187 DOI: 10.1177/1756283X13477715]
- 56 **Rogler G**, Vavricka S. Anemia in inflammatory bowel disease: an under-estimated problem? *Front Med (Lausanne)* 2014; **1**: 58 [PMID: 25646159 DOI: 10.3389/fmed.2014.00058]
- 57 **Kaniewska M**, Bartnik W, Gonciarz M, Kłopocka M, Linke K, Małacka-Panas E, Radwan P, Reguła J, Rydzewska G. Iron deficiency anaemia in patients with inflammatory bowel disease: National Consultant for Gastroenterology Working Group Recommendations. *Prz Gastroenterol* 2014; **9**: 259-263 [PMID: 25395998 DOI: 10.5114/pg.2014.46159]
- 58 **Bernstein CN**, Ament M, Artinian L, Ridgeway J, Shanahan F. Milk tolerance in adults with ulcerative colitis. *Am J Gastroenterol* 1994; **89**: 872-877 [PMID: 8198097]
- 59 **Strisciuglio C**, Giannetti E, Martinelli M, Sciorio E, Staiano A, Miele E. Does cow's milk protein elimination diet have a role on induction and maintenance of remission in children with ulcerative colitis? *Acta Paediatr* 2013; **102**: e273-e278 [PMID: 23445275 DOI: 10.1111/apa.12215]
- 60 **Gupta R**, Makharia G, Khadgawat R, Yadav RK. Evaluation of lactose and milk intolerance, and bone mineral density in Indian patients with inflammatory bowel disease. *Natl Med J India* 2012; **25**: 327-331 [PMID: 23998861]
- 61 **Hlavaty T**, Krajcovicova A, Koller T, Toth J, Nevidanska M, Huorka M, Payer J. Higher vitamin D serum concentration increases health related quality of life in patients with inflammatory bowel diseases. *World J Gastroenterol* 2014; **20**: 15787-15796 [PMID: 25400464 DOI: 10.3748/wjg.v20.i42.15787]
- 62 **Abraham BP**, Prasad P, Malaty HM. Vitamin D deficiency and corticosteroid use are risk factors for low bone mineral density in inflammatory bowel disease patients. *Dig Dis Sci* 2014; **59**: 1878-1884 [PMID: 24619280 DOI: 10.1007/s10620-014-3102-x]
- 63 **Jørgensen SP**, Agnholt J, Glerup H, Lyhne S, Villadsen GE, Hvas CL, Bartels LE, Kelsen J, Christensen LA, Dahlerup JF. Clinical trial: vitamin D3 treatment in Crohn's disease - a randomized double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2010; **32**: 377-383 [PMID: 20491740 DOI: 10.1111/j.1365-2036.2010.04355.x]
- 64 **Pappa HM**, Mitchell PD, Jiang H, Kassiff S, Filip-Dhima R, DiFabio D, Quinn N, Lawton RC, Bronzwaer ME, Koenen M, Gordon CM. Maintenance of optimal vitamin D status in children and adolescents with inflammatory bowel disease: a randomized clinical trial comparing two regimens. *J Clin Endocrinol Metab* 2014; **99**: 3408-3417 [PMID: 24926949 DOI: 10.1210/jc.2013-4218]
- 65 **Dadaei T**, Safapoor MH, Asadzadeh Aghdai H, Balaii H, Pourhoseingholi MA, Naderi N, Zojaji H, Azimzadeh P, Mohammadi P, Zali MR. Effect of vitamin D3 supplementation on TNF- α serum level and disease activity index in Iranian IBD patients. *Gastroenterol Hepatol Bed Bench* 2015; **8**: 49-55 [PMID: 25584176]
- 66 **Ananthakrishnan AN**, Cagan A, Gainer VS, Cheng SC, Cai T, Szolovits P, Shaw SY, Churchill S, Karlson EW, Murphy SN, Kohane I, Liao KP. Higher plasma vitamin D is associated with reduced risk of Clostridium difficile infection in patients with inflammatory bowel diseases. *Aliment Pharmacol Ther* 2014; **39**: 1136-1142 [PMID: 24641590 DOI: 10.1111/apt.12706]
- 67 **Ananthakrishnan AN**, Cheng SC, Cai T, Cagan A, Gainer VS, Szolovits P, Shaw SY, Churchill S, Karlson EW, Murphy SN, Kohane I, Liao KP. Association between reduced plasma 25-hydroxy vitamin D and increased risk of cancer in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2014; **12**: 821-827 [PMID: 24161349 DOI: 10.1016/j.cgh.2013.10.011]
- 68 **Kunachowicz H**, Nadolna I, Przygoda B, Iwanow K. Tabela składu i wartości odżywczej żywności. Wydawnictwo Lekarskie PZWL: Warszawa, 2005
- 69 **Guandalini S**. Are probiotics or prebiotics useful in pediatric irritable bowel syndrome or inflammatory bowel disease? *Front Med (Lausanne)* 2014; **1**: 23 [PMID: 25593899 DOI: 10.3389/fmed.2014.00023]
- 70 **Shen J**, Zuo ZX, Mao AP. Effect of probiotics on inducing remission and maintaining therapy in ulcerative colitis, Crohn's disease, and pouchitis: meta-analysis of randomized controlled trials. *Inflamm Bowel Dis* 2014; **20**: 21-35 [PMID: 24280877 DOI: 10.1097/01.MIB.0000437495.30052]
- 71 **Miele E**, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. *Am J Gastroenterol* 2009; **104**: 437-443 [PMID: 19174792 DOI: 10.1038/ajg.2008.118]
- 72 **Bourreille A**, Cadiot G, Le Dreau G, Laharie D, Beaugerie L, Dupas JL, Marteau P, Rampal P, Moysé D, Saleh A, Le Guern ME, Galmiche JP. Saccharomyces boulardii does not prevent relapse of Crohn's disease. *Clin Gastroenterol Hepatol* 2013; **11**: 982-987 [PMID: 23466709 DOI: 10.1016/j.cgh.2013.02.021]
- 73 **Guslandi M**, Mezzi G, Sorghi M, Testoni PA. Saccharomyces boulardii in maintenance treatment of Crohn's disease. *Dig Dis Sci* 2000; **45**: 1462-1464 [PMID: 10961730]
- 74 **Guslandi M**, Giollo P, Testoni PA. A pilot trial of Saccharomyces boulardii in ulcerative colitis. *Eur J Gastroenterol Hepatol* 2003; **15**: 697-698 [PMID: 12840682]
- 75 **Gupta P**, Andrew H, Kirschner BS, Guandalini S. Is lactobacillus GG helpful in children with Crohn's disease? Results of a preliminary, open-label study. *J Pediatr Gastroenterol Nutr* 2000; **31**: 453-457 [PMID: 11045848]
- 76 **Bousvaros A**, Guandalini S, Baldassano RN, Botelho C, Evans J, Ferry GD, Goldin B, Hartigan L, Kugathasan S, Levy J, Murray KF, Oliva-Hemker M, Rosh JR, Tolia V, Zhouludev A, Vanderhoof JA, Hibberd PL. A randomized, double-blind trial of Lactobacillus GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. *Inflamm Bowel Dis* 2005; **11**:

833-839 [PMID: 16116318]
77 **Prantera C**, Scribano ML, Falasco G, Andreoli A, Luzi C.
Ineffectiveness of probiotics in preventing recurrence after

curative resection for Crohn's disease: a randomised controlled
trial with Lactobacillus GG. *Gut* 2002; **51**: 405-409 [PMID:
12171964]

P- Reviewer: Daniel F, Romano C **S- Editor:** Ma YJ
L- Editor: Roemmele A **E- Editor:** Liu XM

