Scholars Academic Journal of Pharmacy
Abbreviated Key Title: Sch Acad J Pharm
ISSN 2347-9531 (Print) | ISSN 2320-4206 (Online)
Journal homepage: http://saspublishers.com

OPEN ACCESS

Pharmacy

A Common Supplement Used in Inflammatory Bowel Disease

Prashant Singh[1*], Navneet Kumar Verma[2], Raveesh Kharwar[3], Shail Kumari[3], Shivam Jaiswal[3], Satyam Bhardwaj[3]

[1]Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur (U.P.), India-273209
[2]Associate Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur (U.P.), India-273209
[3]Students of B. Pharmacy, Buddha Institute of Pharmacy, GIDA, Gorakhpur (U.P.), India-273209

DOI: 10.36347/sajp.2024.v13i06.007 | **Received:** 29.04.2024 | **Accepted:** 03.06.2024 | **Published:** 05.06.2024

***Corresponding author:** Prashant Singh
Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur (U.P.), India-273209

Abstract **Review Article**

Inflammatory bowel disease (IBD) is a chronic disease of the intestines. IBD, including Crohn's disease and ulcerative colitis, are characterized by a complex interplay of environmental, genetic, and immunological variables. Inflammatory bowel disease (IBD) is caused by the interplay of a person's immune system with precipitating environmental variables, which in people with a genetic predisposition causes an abnormally persistent inflammatory response. The pattern and severity of dietary deficits linked to IBD vary on the level, duration, and activity of the inflammation. However, there is little evidence that dietary changes can modify the course of IBD, and there are no evidence-based dietary recommendations for IBD patients. As a result, patients look to non-medical sources for nutritional advice, such as patient support groups and unreliable websites. The purpose of this review is to discover patient-specific dietary recommendations for IBD and to evaluate their nutritional value. We examine patient-specific dietary data for IBD from popular defined diets and structured internet searches. Dietary advice for specific patients focuses on.

Keywords: Inflammatory bowel disease (IBD), Immune system, Nutrition.

INTRODUCTION

The two main phenotypes of inflammatory bowel diseases (IBD) are ulcerative colitis (UC) and Crohn's disease (CD). These illnesses have a complex etiology that is influenced by multiple factors, including the the external environment, the immune system, and the intestinal flora. Genetic loci linked to IBD have been identified through genome-wide association studies; the majority of these loci show overlapping risk in CD and UC [1, 2]. 163 genetic risk loci have been found as of this writing [3]. These genes cause gastrointestinal immune system malfunction and are implicated in the pathophysiology of IBD System and barrier function, and it is anticipated that the genes may indirectly influence the intestinal microbiome's (the human intestine's composite microbial communities) populations. The majority of risk alleles only slightly raise the chance of IBD, demonstrating the significant influence that the environment plays in the pathophysiology. Additionally, monozygotic twin concordance rates of 10%–15% in UC and 30%–35% in CD highlight the significance of genetics and show limited penetration in both disease subgroups [2]. Unidentified environmental variables may predispose certain children to earlier-onset disease, as the genes linked to pediatric-onset IBD are generally comparable to those linked to adult-onset disease [4]. Children might be exposed to environmental pollutants less frequently, over shorter periods of time, and in smaller amounts overall. hence identifying environmental dangers in young children with IBD may be easier. However, because juvenile IBD is very uncommon, few large studies have thoroughly evaluated environmental factors that may be related. This piece will examine the environmental elements reported in the literature, with an emphasis on early-life exposures that predispose to the start of IBD in children.

Various dietary and nutritional factors have been suggested as being significant etiological factors both for CD and UC, but at the same time, and more importantly, nutrition itself has proven to be a central component in the treatment of the disease, both as a primary therapy and for correcting the various nutritional deficiencies shown by these patients [5]. This report addresses these matters through a literature review, adding certain recommendations for the nutrition management of patients with IBD in the light of the evidence available. Nutritional therapy, which encompasses preventing osteoporosis, treating malnutrition and micronutrient deficiencies, and treating

patients with IBD, is unquestionably vital. children's encouragement of healthy development and growth [6, 7].

DIET IN IBD

Three crucial elements interact to cause inflammatory bowel disease (IBD): an individual's environment, immune system, and genetic susceptibility [8]. The nutritional environment and the local microenvironment (enteric microbiota) can both be considered environmental influences. Although there is insufficient evidence to prove that a person's diet causes CD or UC, over the past few decades, a number of studies have indicated the possible etiological role played by specific feeding practices, based on the correlation between the rise in the incidence of IBD in developed nations and the emergence of new feeding habits in these areas.[9] New feeding practices associated with these lifestyles include the feeding of children cow's milk and large amounts of refined Sugar and fat are consumed in greater quantities than dietary fiber, fruit, and vegetables.

Numerous research studies have demonstrated that breastfeeding lowers the risk of developing CD [10, 11] and UC [12–13]. Even in the instance of babies who were nursed for a Compared to the group that was breastfed for a longer duration, the incidence of CD was markedly higher in a short amount of time [11]. The etiology of IBD has also been linked to the consumption of cow's milk [14]. It has been observed that these patients had higher levels of serum antibodies against the protein found in cow's milk compared to healthy controls [15], and that there was a correlation between the levels of particular antibodies and the index of activity in the case of adult CD patients [16]. Although other research have not found a connection between breastfeeding and IBD, a number of theories offer explanations. Regarding the protective mechanisms of breastfeeding against IBD, these include the following: delaying contact with cow's milk and other allergens and potentially infectious agents; stimulating the development of the gastrointestinal mucosa and its immunological capacity in children [17, 18], and providing protection from gastrointestinal infections [19]. There have been recent suggestions on the potential etiological significance of *Mycobacterium aviumpara* tuberculosis as an infectious agent causing CD [20]. This pathogen, which comes from diseased cows, may spread through milk and be resistant to pasteurization [21]. But there are a few objections to the provided, including the lack of epidemiological evidence for transmissible infection, the lack of therapeutic effectiveness of conventional antimycobacterial drugs, and the low incidence of IBD in poor nations, as evidence for the probable role of M. aviumparatuberculosis in the pathogenesis of CD [22].

A lot of sugar and refined carbs are consumed in these new feeding practices. Numerous research conducted since the 1970s have shown the high levels of usage of these products in IBD patients [23], to the point where they are now thought to be a risk factor for UC [24] and CD [25]. On the other hand, eating vegetables, fruit juices, and citrus fruits may reduce your chance of developing either of the two diseases. One study even found a negative correlation between eating bran and the onset of CD [26]. It has not been feasible to ascertain to this day whether the potentially protective effect results from the action of the dietary fiber or other micronutrients found in fruits and veggies. Several writers have proposed the use of low-refined-carb diets in the treatment of CD, however thorough clinical trials have not supported the advantages of this approach [27].

The lipid components of the diet have received extra attention in recent years due to their potential as IBD causes. Ever before the first epidemiological connections were studies have linked new consumption habits, including fast food, to an increased risk in the development of CD and U [28]. It has also been established that a correlation exists between the consumption of partly hydrogenated fats (margarine) and granulomatous ileitis and UC. Furthermore, consuming high levels of polyunsaturated and monounsaturated fats are linked to an increased risk of UC [29]. Research on the anti-inflammatory qualities of n-3 polyunsaturated fatty acids (PUFAs) was prompted by the finding that Greenland's Eskimos, who ingest high levels of PUFAs from fish oils, have a low prevalence of IBD [30] as opposed to pro-inflammatory omega-6 polyunsaturated fats. Since they alter the metabolism of arachidonic acid by elevating the synthesis of, the latter have been linked in the genesis of IBD. leukotriene B4, a substance that causes inflammation. These findings have created new avenues for research on how lipids in the diet can control inflammatory processes in various diseases because they are an essential part of cell membranes, particularly lymphocyte membranes, which control immune system reactions [31].

Notable are the short-chain fatty acids (SCFAs), of which butyrate is the most representative. These are produced during the intestinal fermentation process of other indigestible carbs and dietary fiber. The physiopathology of UC has been linked to a quantitative SCFA shortage or their oxidation by colonocytes [32], and patients with the condition also have reduced levels of SCFA in vivo oxidation. Even with the information available at this time, there is still a dearth of conclusive proof linking specific food ingredients to the genesis of IBD. Despite this, the facts above force us to acknowledge that significant shifts in the epidemiology of IBD in developed nations have coincided with changes in the content and features of the food that characterize modern life. But we also need to keep in mind that, in addition to our nutrition, our modern lifestyle includes other elements whose potential etiological significance in IBD has not been thoroughly investigated [33].

NUTRITIONAL DEFICIENCY IN IBD

An important aspect of IBD care is nutrition assessment, which combines a clinical examination, laboratory testing, and history-taking (e.g., serum albumin and iron studies) [34, 35]. There exist multiple malnutrition indicators, none of which are exclusive. The two most significant indicators are body mass index (BMI) and weight loss; however, a recent research found that IBD patients who met the conventional clinical criteria for well-being (BMI) still had reduced muscle mass [36]. A more thorough evaluation that incorporates anthropometry and scoring methods like the Nutrition Risk Screening (which takes taking into account the degree and length of weight loss, the Body Mass Index (weight in kg/height in m^2) for adults, percentile charts for kids, food intake (appetite and capacity to consume and hold food), and "stress factors" (impact of medical condition on nutritional requirements)[37]Based on a standardized questionnaire, the Subjective Global Assessment (SGA) is a clinical nutritional indicator that evaluates gastrointestinal symptoms, functional capacity, recent changes in body weight, and dietary consumption changes and physical indicators of malnutrition (such as ascites, edema, or loss of muscle mass or subcutaneous fat) are also commonly employed to assess malnutrition [38]. Furthermore, a number of molecular indicators may be useful in identifying malnutrition (Table 1) However, albumin and prealbumin are negative acute phase proteins, and they decrease with an inflammatory response, independent of malnutrition. Thus, hypoalbuminemia in IBD patients could reflect active disease rather than protein-energy malnutrition. Also, transferrin an acute phase protein that has been proposed as a good measure of protein status could have limited value in patients with IBD, considering that the high prevalence of inflammation and iron deficiency act as confounding factors [39].

Protein-Energy Malnutrition

A condition known as malnutrition is when an organism's structural and functional development is disrupted, leading to an imbalance in the requirements, intake, and utilization of nutrients. The length, intensity, and anatomical scope of the illness determine the pattern and degree of malnutrition [35].

There have been widely differing reports regarding the prevalence of malnutrition in various IBD patient types at various stages of the disease. According to reports, the prevalence is 20%.85% of hospitalized patients, and roughly 14% and 5.7% of CD and UC patients, respectively, in terms of prevalence [36, 40]. Moreover, because the two disorders affect distinct body parts (small bowel vs. rectum), malnutrition is more common in CD patients (50-70%, with 65e75% of CD patients underweight at presentation) [35] than in UC patients (18-62%). Of hospitalized patients with CD and UC, hypoalbuminemia is seen in 25-80% and 25-50% of cases, respectively [34].

Malnutrition in patients with CD typically develops gradually over time (and is therefore associated with the length of sickness); in contrast, malnutrition in patients with UC develops quickly in cases that are worsened (and is therefore associated with the activity of illness) [40]. Malnutrition based on protein and calories is caused by a number of reasons in IBD [41]. Due to the induction of anorexia and cachexia by pro-inflammatory cytokines, such as TNFalpha, inflammatory mediators, including disease activity, are frequently associated with a decreased nutritional supply. Moreover, a relative lack of energy or protein can be caused by malabsorption, maldigestion, increased energy expenditure, and gastrointestinal protein loss. This can lead to overt malnutrition in adults and growth failure or inadequate weight gain in infants.

Micronutrient Depletion

IBD patients have a wide range of vitamin and mineral deficiencies, differing in their clinical significance. The effects of micronutrient deficiencies on anemia, bone mineral density, thrombophilia, wound healing, and carcinogenesis are particularly relevant to doctors.

Anemia

Anemia is the most prevalent systemic consequence of IBD, with historical cohorts of hospitalized IBD patients reporting rates ranging from 40% to 70% [42, 43] more current research employing population-based information on outpatient IBD patients 18% to 25% of people in Switzerland and Scandinavia were found to have anemia [44]. Even though anemia has been demonstrated to have an impact on patients' quality of life and capacity for employment, gastroenterologists frequently ignore it [45]. Iron, folic acid, or vitamin B12 deficiency can cause anemia, as can chronic inflammation (chronic illness anemia) and/or drug side effects (azathioprine, 6-mercaptopurine, methotrexate, or sulfasalazine).

Iron

Iron deficiency, which affects 36% to 90% of people with IBD, is the primary cause of anemia in this population [46]. An insufficient intake of food (avoidance) might result in an iron deficit. of leafy greens and/or vegetarian diets), persistent gastrointestinal bleeding, and—above all—deficit in absorption and utilization. The duodenum and proximal jejunum are the main sites of normal iron absorption. The amount absorbed from food sources varies from 5% to 35%, depending on the patient's iron reserves and the type of iron consumed [47]. Generally speaking, iron from animal sources in the form of heme is more readily absorbed, but iron from salt ($Fe^{2+,}$ $Fe^{3+)}$ is lower, depends on the existence of an acidic environment, and can be thwarted by concurrent use of antacids or proton pump inhibitors. Even with adequate food consumption and/or supplementation, people with active IBD may experience impaired iron metabolism. Hepcidin is

upregulated in response to proinflammatory stimuli such lipopolysaccharide, IL-6, and TNF-a. a crucial mediator in iron homeostasis that promotes iron retention in macrophages and monocytes and prevents iron from leaving enterocytes and entering the circulation. The latter method is especially essential as 90% of daily iron storage derive from recycling of iron from senescent red blood cells by macrophages. Elevated ferritin levels are a common indicator of iron retention in macrophages, the primary circulating iron-storing protein in the body [48].

Iron-deficiency anemia has been linked to reduced physical activity, weariness, and a worse quality of life in individuals with inflammatory bowel disease (IBD), as well as poorer cardiac and renal function in the general population. Additionally, it has been more recently linked to restless leg syndrome, a condition that is more prevalent in CD patients than in the general population [49]. The best long-term treatment strategy for iron-deficiency anemia is, wherever feasible, to effectively control the underlying ailment. Direct iron supplementation is typically advised for individuals with overt anemia (haemoglobin <13 g/dL in males and < 12 g/dL in females) when this is not achievable or not anticipated to happen soon [50]. The use of iron supplementation is more debatable in situations of iron insufficiency without anemia. Iron tests ought to be performed on people who are highly susceptible to anemia. be properly watched, and short-term nutritional interventions such as increasing dietary iron, taking ascorbic acid concurrently, and stopping proton-pump inhibitor or H2-antagonist medication may be considered.

Folate

A macrocytic megaloblastic anemia can result from deficiencies in folic acid (vitamin B9) because folate is essential for DNA synthesis and healthy erythrocyte division. In contrast to iron, the body stores an average of only 500–20,000 lg of dietary folate. in healthy individuals. Therefore, reserves of folic acid can be quickly depleted if the DRI of 400–1000 lg is not consumed [51]. In nations like the United States and Canada, where federal regulations have mandated folate supplementation in cereals and other enriched grain products to decrease neural tube birth defects, rates of folic acid deficiency have dramatically decreased within the general population over the last two decades [52]. Despite these folate fortification initiatives, folic acid deficiency may still be more common in IBD patients than in the general population. Although more recent Even though studies show that the prevalence of folate deficit is lower than that found in earlier IBD cohort studies (51%–80%),14 folate deficiency still seems to be very widespread, especially in CD. In a 2010 retrospective casecontrol research, aberrant serum folate levels (<3 ng/mL) were discovered in 28.8% of patients with CD, 8.8% of patients with ulcerative colitis (UC), and 3% of controls [51]. Similar rates (20%–26%) of subnormal whole-blood folate levels were reported in three CD investigations, one of which exclusively included patients with the illness in remission [53, 54]. It should be mentioned that every study mentioned above employed Serum folate levels, which represent average folate levels over the previous three months, may be a more accurate test than red blood cell (RBC) folate levels. Two investigations using RBC folate levels in IBD patients have shown significantly lower rates of deficiency (0%–7%) [55].

Vitamin B12

Vitamin B12 (cobalamin) deficiency is less frequent than folate deficiency in the general population, but it is particularly important to take into account in CD and older IBD patients. It is also linked to megaloblastic anemia [56]. Active vitamin B12 absorption occurs only in the terminal ileum, in contrast to other water-soluble vitamins that are absorbed in the proximal small bowel. Humans get their B12 primarily from animal sources, and the process of gastrointestinal absorption is somewhat intricate. Pancreatic proteases break dietary cobalamin from R factor so that it can attach to intrinsic factor, which is created in the stomach. Following its passage to the ileum, the IF-cobalamin complex binds to the particular cobalamin receptor before being absorbed through the distal ileal mucosa. A deviation from the norm at any point can result in B12 malabsorption.

Historically, clinical evidence and low serum vitamin B12 levels—typically less than 200 pg/mL (150 pmol/L)—have been used to diagnose vitamin B12 deficiency. of illness. Even in the absence of hematological signs of a B12 shortage, many people, especially elderly patients, may experience irreversible neuropsychiatric manifestations.44 Since these tend to be more sensitive than serum B12 levels, it is advised that methylmalonicacid and homocysteine levels—metabolites of vitamin B12—be evaluated next in at-risk populations if serum B12 levels are normal [57].

Calcium

With an average body reserve of 1-2 kg, calcium is the most prevalent mineral in humans, with 99% of that being found in the bones. The typical range for extracellular calcium regulation is 2.2–2.6 mmol/L, or 9–10.5 mg/dL. through the interaction of calcitonin and parathyroid hormone, which controls the activity of the vitamin D system, the primary inducer of the intestinal tract's active calcium absorption. Calcium is mostly absorbed through the intestines in the duodenum and proximal jejunum. There are two ways that calcium is absorbed: 1) an uncontrolled paracellular pathway that is mostly dependent on food consumption2) an active intracellular pathway via calcium channels, the transcription of which is reliant on 1,25-vitamin D (1,25-OHD) and luminal calcium concentration. Furthermore, it is unknown how calcium is secreted in the colon and the distal small bowel (distal jejunum and ileum). Volume 18, Number 10, October 2012, Inflamm Bowel Dis Micronutrient Deficits in Mechanisms of IBD 196.

Although the exact degree has not been thoroughly investigated, diarrhea and malabsorption are probably worsening intestinal calcium losses [58].

For the majority of IBD patients, calcium supplements should be taken at doses of 1000–1500 mg daily (1000 mg for women 25 years of age and older and men 65 years of age and younger). aged; 1300 mg for females aged 18 to 25; 1500 mg for women who have gone through menopause and males older than 65). Studies assessing the effectiveness of calcium supplementation alone or in conjunction with vitamin D supplementation are comparatively rare. Though there was no change in the frequency of fractures, it did appear from two observation cohorts that calcium at 1000 mg dosages combined with nontreatment levels of vitamin D may have led to a minor improvement in BMD after a year [59, 60].

Vitamin D

Due to its ability to maximize intestinal calcium absorption and promote osteoblastic development, vitamin D is a fat-soluble vitamin that is crucial for normal bone mineralization. Elevated indicators of bone resorption and secondary hyperparathyroidism have been linked to low vitamin D levels. of bone turnover (uncarboxylatedosteocalcin and alkaline phosphatase) in hypovitaminosis D-positive patients with IBD and healthy individuals in comparison to normal controls [61]. Nevertheless, whereas vitamin D levels have been linked to BMD in the general population, this relationship has not been as consistently proven in cohorts with IBD, possibly because since there is a lack of data and a multitude of pathways underlying bone damage in IBD [62].

The general population's vitamin D status is usually not constant and can change with the season, latitude, time of day, skin pigmentation, age (because of declining amounts of cutaneous 7-hydrocholesterol), smoking, and sunscreen use (SPF 30 prevents 95% of skin production) [62]. In the northern hemisphere, vitamin D deficiency (defined as blood 25-OHD levels ~15 ng/mL) and insufficiency (~20 ng/mL) are quite common in healthy people and children, especially during the winter. Hypovitaminosis D has been shown to be more common in IBD patients, with rates ranging from 22% to 70% in CD patients and up to 45% in UC patients, according to several investigations [63, 64].

Vitamin K

Although its significance is less obvious than that of vitamin D, vitamin K has been linked to bone health. Although there are several forms of the fat-soluble vitamin K, phylloquinone (vitamin K1), which is found in green Leafy vegetables are the main type of food. Vitamin K is recognized as a cofactor for the posttranslational c-carboxylation of several proteins, such as blood coagulation factors and osteocalcin (OC), which is a regulator of the maturation of bone minerals. Osteoblasts create osteocalcin, which needs to be c-carboxylated in order to bind calcium. When there is a lack of vitamin K, OC is released from the body and stays uncarboxylated. Vitamin K status in the bone is reflected by serum uncarboxylatedosteocalcin (percent or total), which is frequently used as an indirect indicator of total vitamin K reserves. Serum phylloquinone levels are another way to assess vitamin K status, albeit triglyceride levels and recent food consumption can affect levels [65]. The absence of a single trustworthy and straightforward way of One fundamental restriction on interpreting research on the significance of vitamin K for bone health is one's own vitamin K level. Numerous extensive epidemiological studies, such as two that employed the Framingham cohort and the Nurses' Health Study cohort, show that inadequate dietary intake of vitamin K appears to be linked to reduced BMD and the risk of osteoporotic fractures [66-68]. Studies linking bone disease to biochemical markers of vitamin K (serum phylloquinone levels or uncarboxylatedosteocalcin level) have, however, proven less reliable. While some studies find a correlation, others do not [69, 70]. This most likely indicates a limited correlation between vitamin K status and bone disease, or the limits of the vitamin K status assays available today.

Vitamin C

Ascorbic acid, or L-ascorbic acid, is another name for vitamin C. It functions as a cofactor in a number of enzymatic activities and is a significant antioxidant in a variety of tissues. Vitamin C has a significant role in wound healing by promoting angiogenesis and controlling neutrophil activity [71]. Clinical scurvy, which is characterized by bleeding gums, hemarthroses, and poor wound healing, can be the outcome of a severe deficit. In IBD, less severe deficits are relatively common, as indicated by subnormal serum vitamin C levels [72, 73]. Both active and passive transport are used in the jejunum to absorb vitamin C, although deficiencies seem to be equally common in people with UC or CD and are independent of illnessactivity [53]. It is more likely that inadequate vitamin C intake which has been shown in several IBD cohorts, including those in remission is the primary mechanism underlying vitamin C shortage [72]. For individuals with urgent wound healing needs, such as those with fistulas, vitamin C supplementation at a dose of 100 to 200 mg/d is advised or a recent medical procedure [71].

Zinc

Zinc is a necessary mineral that is needed for the catalytic activity of over 100 enzymes, including metalloproteinases. It is also crucial for wound healing, immunological response, and the creation of collagen and proteins. Intake of zinc occurs along the by a poorly understood transport system that travels the entire length of the small intestine, although it is also eliminated through intestinal and pancreatic secretions. It is believed that people with persistent diarrhea, malabsorption, and

hypermetabolic conditions (sepsis, burns) are somewhat likely to be zinc deficient.

For men, the current USDA recommended daily zinc consumption is 11 mg, and for women, it is 8 mg. Patients with severe diarrhea (>300 g of stool/day) may benefit from taking 20–40 mg of zinc gluconate daily.146 Zinc supplementation of 40 mg of elemental zinc (176 mg zinc sulfate) for 10 days has been proposed to improve wound healing. Adults have traditionally taken 220 mg of zinc sulfate twice day (25–50 mg of elemental zinc). Such amounts shouldn't be administered for longer than two to three weeks unless patients have severe, persistent diarrhea since too much zinc might obstruct the absorption of iron and copper, which can result in a deficit of these vital minerals [71].

Nutritional Therapeutic Approaches

Dietary Interventions

Currently, there are no guidelines for treating IBD other than adhering to a healthy and varied diet, despite some studies suggesting that dietary factors may have a role in the onset and course of the condition. most patients. When IBD flares up suddenly, prescribing a low-residue, low-insoluble fiber diet may be prudent, especially for individuals who have stricturing CD or severe UC bouts. There have been a number of theories put up recently regarding the potential for certain nutrients to regulate inflammation. In specifics, it has been proposed that the anti-inflammatory properties of omega-3 fatty acids, or fish oil, are advantageous in chronic inflammatory diseases such inflammatory bowel disease.[75] Currently, information is mostly accessible regarding the advantages of fermentable fiber, which is the primary source of short-chain fatty acids (SCFA), and n-3 polyunsaturated fatty acids (PUFAs) during the remission/quiescent phase of both UC and CD. When compared to their n-6 PUFA counterparts [76], 3 PUFAs are converted to produce 3-series prostaglandins, thromboxanes, and 5-series leukotrienes, which typically cause less inflammation and have anti-inflammatory properties. Nevertheless, a recent systematic review [77] states that omega 3 therapy for IBD patients is not recommended due to a lack of data, despite a slight yet considerable advantage of n-3 therapy for preserving remission and a significant level of safety have been documented. Fermentable fiber is fermented by colonic microflora and produces numerous compounds, including SCFA, primarily butyrate, which can be beneficial in inflammatory bowel disease. It also produces a lot less residue than insoluble fiber. The primary metabolic substrate for colonic epithelial cells is butyrate, and there are in vitro indications that, indicating that butyrate has the capacity to inhibit the synthesis of pro-inflammatory cytokines, to encourage the restoration of the intracellular ROS balance, and to activate NF-kB.[78] Furthermore, rectal injection of butyrate or combinations of SCFA has been demonstrated to reduce inflammation in patients with active UC, based on multiple in vivo investigations [78]. However, Kovarik *et al.*, discovered showed when triggered via toll-like receptor (TLR) 2 engagement, peripheral blood monoclast cells (PBMC) from IBD patients are less responsive to the inhibitory action of n-butyrate than healthy persons [79]. Because we still don't fully understand the pathogenic mechanisms underlying the development of IBD, the data that are currently available regarding nutritional interventions are not always consistent. As a result, more research is required to enhance the nutritional therapeutic approach and produce unique nutritional guidelines.

Enteral Nutrition (EN)

Enteral nutrition (EN) has been studied either as nutritional support against malnutrition or as the primary therapy for CD because it may help to control disease activity [79].

EN for Nutritional Support

EN has specific implications as nutritional assistance. Severe malnutrition, moderate malnutrition with food intake predicted to be insufficient for more than five days, and average nutritional status with insufficient food intake more than ten days are the conditions under which it should be employed days or hypercatabolism that is mild to severe [81, 82].

When it comes to nutritional replacement, EN is favored over parenteral nutrition (PN) due to its decreased risk of major consequences and reduced expense. Furthermore, it has been demonstrated that the existence of luminal nutrients plays a crucial trophic factor for intestinal mucosa, potentially preserving gastrointestinal function and preventing bacterial translocation. Massive bleeding, intestinal blockage, bowel perforation, short bowel syndrome, and toxic megacolon are among the conditions that preclude the use of enteral feeding. When EN is not recommended, PN needs to be supplied instead [83].

Furthermore, research is being done on EN's potential long-term benefits. Nutritional therapy has recently been proposed as a potential means of reducing mucosal inflammation [84], although the pathogenetic Mechanisms are yet not fully understood. In particular, whereas steroids seem to be unsuccessful in encouraging mucosal healing, there is accumulating data suggesting positive long-term effects of nutrition on mucosal healing and the normalization of inflammatory indicators, with rates between 44 and 74% [84]. Additionally, it has been demonstrated that additional EN is useful in helping CD patients maintain remission, which suggests that it has a suppressive effect on endoscopic and clinical disease activity.

There are currently few data on dietary support for UC patients, especially when it comes to nutrition therapies and UC patients' ability to maintain remission. Malnutrition is less frequent when there is UC, which is primarily seen in individuals with actively deteriorating

conditions that are unresponsive to conventional medical treatment.3 It is thought to be a separate risk factor for the consequences of surgery [85].

EN as Primary Therapy

Because of EN's anti-inflammatory properties, which typically indicate an improvement in nutritional status (i.e., normalization of inflammatory markers within three days), it may be a useful therapeutic method for CD. Forty Numerous methods have been suggested, however none has been shown to be the main method of action [81]. EN may promote intestinal trophism, alter bowel movements, and supply caloric nutritional support with a low antigenic load (semi- and elemental diet) and minimal fat (especially with low levels of ueicosanoids, in favor of relatively high concentrations of). flora, and/or encourage "intestinal rest" (because the jejunum absorbs EN-available combinations fully) [86].

It is questionable if EN is a truly effective therapy method for CD, notwithstanding the pathophysiological presumptions. Numerous investigations, comprising meta-analyses, have been released in the literature, however opinions on the findings have been divided. Four of the six published meta-analyses state that corticosteroids are more successful than EN in treating active CD [87, 88], whereas the two other studies—which only include trials involving children—state that steroids are equally effective in treating CD [89, 90]. Based on the evidence at hand, it is probable that a number of additional patient and illness variables influence decisions for therapeutic management. It might offer the option of enteral nutritional treatment. Consequently, insufficient information is available to support or contradict EN based on the meta-analyses' findings. Consequently, EN would mostly be used as nutritional support for adults who are malnourished, typically in conjunction with steroids, which are thought to be the gold standard treatment for CD. However, EN might take the lead in the pediatric context, when corticosteroids should be avoided because to their toxicity.

Nonetheless, there is ongoing discussion over the disparate outcomes seen in adult and pediatric groups. First off, the age and disease localization of the published data are from two distinct groups (the majority of children have ileal CD, which is more common likely to benefit from EN as the main therapy strategy), the length of the illness (most pediatric studies cover initial diagnosis), and the strong adherence to EN (which is considerably better in the pediatric scenario).

A prospective research by Hanai et al. was been released to evaluate EN as a secure and reliable substitute for immunomodulator drugs. According to the study, EN is an effective maintenance treatment for patients with CD. With less adverse effects and almost as well as 6-mercaptopurine, it is a safe option for long-term maintenance treatment [91].

Furthermore, randomized trials that directly compare nutritional intervention to a placebo are uncommon, which means that the question of whether EN is more helpful than a placebo in adults is still up for debate. Still, Comparing EN efficacy, which has been reported to be about 40%, to the remission rate (about 25%) in the placebo group in other CD medication trials These findings imply, however indirectly, that EN is useful in bringing about remission [90]. Regardless, even in pediatric patients, where EN is regarded as a first-line treatment due to its strong ability to induce remission, positive effects on growth, and There are fewer side effects, and there are no particular recommendations for enteral formula selection. It is necessary to conduct more research on various enteral formulations (elemental, immuno-nutrition, gut-specific nutrients), as well as enteral and pharmacological therapy combinations.

In severe acute cases of UC, although there are no data supporting a nutritional approach as a first-line therapy, EN may play a significant role, whereas PN is reserved for patients in whom EN is contraindicated or likely to fail.

Parenteral Nutrition

The primary indication for PN in IBD patients is to address malnourishment. Given that EN has been demonstrated to be at least as effective as PN while having fewer negative effects and a cheaper cost, the current recommendation for Only a select few IBD patients for whom enteral feeding has failed or is not recommended are eligible for PN assistance [92]. Thirteen Intraintestinal blockage, toxic megacolon, and enterocutaneous fistulas with increased gastrointestinal output (>400 mL/die) are the main indications for pressure necrosis (PN).Furthermore, PN is typically recommended in situations involving gastrointestinal perforations, severe stenotic disease, short bowel syndrome (SBS), and intractable vomiting. Comparing PN to EN, there are no differences in the ways that promote wound healing and small bowel reconstitution. It is believed that feeding will stabilize the small intestine's organic function more quickly [93]. Furthermore, there is no benefit to PN if the illness is persistently active because, in accordance with official standards from the American Gastroenterological Association (AGA), PN rarely results in an enhanced rate of remission. The rate of surgical intervention for CD is unaffected by PN, and avoiding the intestinal route in order to induce clinical remission is ineffective.48 PN assistance may be helpful for both pre- and post-operative nutritional support in patients with CD and UC, as well as in situations of severe malnourishment. It has been demonstrated that using complete PN prior to surgery improves serum albumin and body weight in patients with CD, even though it's unknown how it affects post-operative morbidity and death.[94] Retrospective studies have shown that CD patients supported with pre-operative total PN had a shorter length of bowel requiring resection, better clinical

outcomes, and fewer post-operative complications; however, these advantages came at the cost of an extended hospital stay [95].

Home Parenteral Nutrition

SBS with chronic intestinal failure—which is often the result of multiple small intestine resections due to CD—is the most common reason for home PN in IBD. SBS happens when there is not enough viable jejunum remaining (less than 150–200 cm) to support the absorption of fluids, electrolytes, and nutrients. The length of the residual small bowel and the type of anastomosis in the digestive circuit affect PN dependency in patients with SBS. Small bowel lengths with reported cut-off values of less than 100 cm for end-enterostomy, less than 65 cm for jejunocolic, and less than 30 cm for jejunoileocolic type of anastomosis are used to distinguish between temporary and permanent intestinal failure [96].

Comprehensive patient education and the backing of a committed multidisciplinary team are necessary for home patient care. While home PN provides patients with SBS with potentially life-saving nutritional support, it islinked to substantial morbidity and sometimes fatal consequences (such as those involving the catheter, metabolism, gastrointestinal, hepatic, renal, and skeletal issues), which frequently necessitate hospitalization [97]. According to studies, home PN is strongly linked to bettering serum albumin and transferrin levels, lowering oral steroid reliance, and improving quality of life. On the other hand, it doesn't appear to affect CD patients' body weight or need for surgery [97].

PN as Primary Therapy

Bowel rest, as a result of total parenteral nutrition (TPN), has been found to reduce intestinal inflammation and decrease disease activity in selected patients with CD. Many after-the-fact evaluations have looked at the advantages of TPN as a main treatment for CD, especially for patients who have not responded well to alternative pharmaceutical or dietary approaches, albeit the results are still debatable. About 54% of patients get their first TPN-induced remission and clinical relapses are frequent (happening in roughly 60% of patients receiving TPN therapy after two years) [98]. However, PN does not appear to be a successful initial treatment. treatment UC, since only 12% of patients achieve stable remission over a 12-month period, and the first response rate is 37e41% [98].

CONCLUSION

In the past, dietary inadequacies were thought to be the primary cause of children's development failure, malnutrition, and inability to maintain an appropriate body weight. for people with IBD. While dietary deficiencies remain clinically relevant, especially for children, advances in diagnostics and medical interventions have partially reduced their incidence. The long-term effects of traditional IBD treatments, such as immunosuppressive medications, glucocorticoids, anti-inflammatory pharmaceuticals, and more recently, biologic agents, are still debatable despite their effectiveness in reducing inflammation and causing sustained remission.in certain cases reflecting deleterious consequences on nutrient status. For undernourished IBD patients, nutritional supplementation is recommended either as a supportive When feasible, the enteral route should be used as the initial option or as a strategy. In adults, EN has been demonstrated to be useful in conjunction with corticosteroids which continue to be the cornerstone of treatment—for both active CD and preserving remission.[99] For children, who should not receive long-term steroid medication, nutrition therapy appears to be just as beneficial as steroid therapy. However, the majority of IBD patients continue to experience vitamin deficiency. Its prevalence depends on the extent and the activity of the disease, and it is more commonly observed in CD than in UC patients. Lastly, new research [100] indicates that obesity may be associated with a higher need for surgery, indicating a more severe form of the illness. of course. From this angle, even though there isn't a clear direct action, the addition of steroid medication and inactivity may make the issue worse. It's possible that fat patients' heightened inflammatory response speeds up the development of digestive illnesses. Therefore, a crucial component of the therapy of IBD patients is a thorough nutritional assessment and nutritional support, including EN, PN, and vitamin supplementation, underscoring the significance of treating patients individually through multidisciplinary care.

REFERENCES

1. Homer CR, Richmond AL, Rebert NA, et al. ATG16L1 and NOD2 interact in an autophagy-dependent antibacterial pathway implicated in Crohn's disease pathogenesis. Gastroenterology. 2010;139:1630– 41. 41 e1-2.
2. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011;474:307–17.
3. Brant SR. Promises, delivery, and challenges of inflammatory bowel disease risk gene discovery. ClinGastroenterolHepatol. 2013;11:22–6.
4. Imielinski M, Baldassano RN, Griffiths A, et al. Common variants at five new loci associated with early-onset inflammatory bowel disease. Nat Genet. 2009;41:1335– 40.
5. Lee D, Albenberg L, Compher C, et al. Diet in the pathogenesis and treatment of inflammatory bowel diseases. Gastroenterology 2015; 148:1087–106.
6. Ananthakrishnan AN, Cagan A, Gainer VS, Cai T, Cheng SC, Savova G, et al. Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. Inflamm Bowel Dis 2013 Aug;19(9): 1921e7.

7. Ananthakrishnan AN, Cagan A, Gainer VS, Cheng SC, Cai T, Szolovits P, et al. Higher plasma vitamin D is associated with reduced risk of Clostridium difficile infection in patients with inflammatory bowel diseases. Aliment PharmacolTher 2014 May;39(10):1136e42
8. Shanahan F. Inflammatory bowel disease: immunodiagnostics, immunotherapeutics, and ecotherapeutics. Gastroenterology 2001; 120: 622-635
9. Bernstein CN, Shanahan F. Disorders of a modern lifestyle: reconciling the epidemiology of inflammatory bowel diseases. Gut 2008; 57: 1185-1191.
10. Corrao G, Tragnone A, Caprilli R, Trallori G, Papi C, Andreoli A, Di Paolo M, Riegler G, Rigo GP, Ferraù O, Mansi C, Ingrosso M, Valpiani D. Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. Cooperative Investigators of the Italian Group for the Study of the Colon and the Rectum (GISC). Int J Epidemiol 1998; 27: 397-404
11. Bergstrand O, Hellers G. Breast-feeding during infancy in patients who later develop Crohn's disease. Scand J Gastroenterol 1983; 18: 903-906
12. Acheson ED, Truelove SC. Early weaning in the aetiology of ulcerative colitis. A study of feeding in infancy in cases and controls. Br Med J 1961; 2: 929-933
13. Whorwell PJ, Holdstock G, Whorwell GM, Wright R. Bottle feeding, early gastroenteritis, and inflammatory bowel disease. Br Med J 1979; 1: 382
14. Binder JH, Gryboski JD, Thayer WR Jr, Spiro HM. Intolerance to milk in ulcerative colitis. A preliminary report. Am J Dig Dis 1966; 11: 858-864
15. Lerner A, Rossi TM, Park B, Albini B, Lebenthal E. Serum antibodies to cow's milk proteins in pediatric inflammatory bowel disease: Crohn's disease vs. ulcerative colitis. ActaPaediatrScand 1989; 78: 81-86
16. Knoflach P, Park BH, Cunningham R, Weiser MM, Albini B. Serum antibodies to cow's milk proteins in ulcerative colitis and Crohn's disease. Gastroenterology 1987; 92: 479-485
17. Pittard WB 3rd. Breast milk immunology. A frontier in infant nutrition. Am J Dis Child 1979; 133: 83-87
18. Pittard WB 3rd, Bill K. Immunoregulation by breast milk cells. Cell Immunol 1979; 42: 437-441
19. Beaudry M, Dufour R, Marcoux S. Relation between infant feeding and infections during the first six months of life. J Pediatr 1995; 126: 191-197
20. Hermon-Taylor J. Protagonist. Mycobacterium avium subspecies paratuberculosis is a cause of Crohn's disease. Gut 2001; 49: 755-756
21. Harris JE, Lammerding AM. Crohn's disease and Mycobacterium avium subsp. paratuberculosis: current issues. J Food Prot 2001; 64: 2103-2110.
22. Sartor RB. Does Mycobacterium avium subspecies paratuberculosis cause Crohn's disease? Gut 2005; 54: 896-898
23. Martini GA, Brandes JW. Increased consumption of refined carbohydrates in patients with Crohn's disease. KlinWochenschr 1976; 54: 367-371
24. Mayberry JF, Rhodes J, Newcombe RG. Increased sugar consumption in Crohn's disease. Digestion 1980; 20: 323-326
25. Geerling BJ, Stockbrügger RW, Brummer RJ. Nutrition and inflammatory bowel disease: an update. Scand J GastroenterolSuppl 1999; 230: 95-105
26. Rawcliffe PM, Truelove SC. Breakfast and Crohn's disease- -I. Br Med J 1978; 2: 539-540
27. Ritchie JK, Wadsworth J, Lennard-Jones JE, Rogers E. Controlled multicentre therapeutic trial of an unrefined carbohydrate, fibre rich diet in Crohn's disease. Br Med J (Clin Res Ed) 1987; 295: 517-520
28. Persson PG, Ahlbom A, Hellers G. Diet and inflammatory bowel disease: a case-control study. Epidemiology 1992; 3: 47-52
29. Geerling BJ, Dagnelie PC, Badart-Smook A, Russel MG, Stockbrügger RW, Brummer RJ. Diet as a risk factor for the development of ulcerative colitis. Am J Gastroenterol 2000; 95: 1008-1013
30. Kromann N, Green A. Epidemiological studies in the Upernavik district, Greenland. Incidence of some chronic diseases 1950-1974. Acta Med Scand 1980; 208: 401-406
31. Jeffery NM, Newsholme EA, Calder PC. Level of polyunsaturated fatty acids and the n-6 to n-3 polyunsaturated fatty acid ratio in the rat diet alter serum lipid levels and lymphocyte functions. Prostaglandins LeukotEssent Fatty Acids 1997; 57: 149-160
32. Chapman MA, Grahn MF, Boyle MA, Hutton M, Rogers J, Williams NS. Butyrate oxidation is impaired in the colonic mucosa of sufferers of quiescent ulcerative colitis. Gut 1994; 35: 73-76
33. Simpson EJ, Chapman MA, Dawson J, Berry D, Macdonald IA, Cole A. In vivo measurement of colonic butyrate metabolism in patients with quiescent ulcerative colitis. Gut 2000; 46: 73-77
34. Lucendo AJ, De Rezende LC. Importance of nutrition in inflammatory bowel disease. World J Gastroenterol 2009;15:2081e8.
35. Goh J, O'Morain A. Review article: nutrition and adult inflammatory bowel disease. Aliment PharmacolTher 2003;7:307e20
36. Valentini L, Schaper L, Buning C, Hengstermann S, Koernicke T, Tillinger W, et al. Malnutrition and impaired muscle strength in patients with Crohn's disease and ulcerative colitis in remission. Nutrition 2008;24:694e702
37. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z., Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. ClinNutr 2003;22:321e36

38. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr 1987;11:8e13
39. Valentini L, Schulzke JD. Mundane, yet challenging: the assessment of malnutrition in inflammatory bowel disease. Eur J Intern Med 2011;22:13e5.
40. Han PD, Burke A, Baldassano RN, Rombeau JL, Lichtenstein GR. Nutrition and inflammatory bowel disease. GastroenterolClin North Am 1999;28:423e43.
41. Hartman C, Eliakim R, Shamir R. Nutritional status and nutritional therapy in inflammatory bowel diseases. World J Gastroenterol 2009;15:2570e8
42. Beeken WL. Remediable defects in Crohn disease: a prospective study of 63 patients. Arch Intern Med. 1975;135:686–690.
43. Ormerod TP. Observations on the incidence and cause of anaemia in ulcerative colitis. Gut. 1967;8:107–114.
44. Voegtlin M, Vavricka SR, Schoepfer AM, et al. Prevalence of anaemia in inflammatory bowel disease in Switzerland: a cross-sectional study in patients from private practices and university hospitals. J Crohns Colitis. 2010;4:642–648.
45. Pizzi LT, Weston CM, Goldfarb NI, et al. Impact of chronic conditions on quality of life in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2006;12:47–52.
46. Gasche C, Lomer MC, Cavill I, et al. Iron, anaemia, and inflammatory bowel diseases. Gut. 2004;53:1190–1197.
47. Frazer DM, Anderson GJ. Iron imports. I. intestinal iron absorption and its regulation. Am J PhysiolGastrointest Liver Physiol. 2005; 289:G631–635.
48. Vidal-Alaball J, Butler CC, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev. 2005;3:CD004655.
49. Weinstock LB, Bosworth BP, Scherl EJ, et al. Crohn's disease is associated with restless legs syndrome. Inflamm Bowel Dis. 2010;16: 275–279.
50. Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. Inflamm Bowel Dis. 2007;13:1545–1553.
51. Yakut M, Ustun Y, Kabacam G, et al. Serum vitamin B12 and folate status in patients with inflammatory bowel diseases. Eur J Intern Med. 2010;21:320–323.
52. Honein MA, Paulozzi LJ, Mathews TJ, et al. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. JAMA. 2001;285:2981– 2986.
53. Fernandez-Banares F, Abad-Lacruz A, Xiol X, et al. Vitamin status in patients with inflammatory bowel disease. Am J Gastroenterol. 1989;84:744–748.
54. Hodges P, Gee M, Grace M, et al. Vitamin and iron intake in patients with Crohn's disease. J Am Diet Assoc. 1984;84:52–58.
55. Vagianos K, Bector S, McConnell J, et al. Nutrition assessment of patients with inflammatory bowel disease. JPEN J Parenter Enteral Nutr. 2007;31:311–319
56. McNulty H, Scott JM. Intake and status of folate and related B-vitamins: considerations and challenges in achieving optimal status. Br J Nutr. 2008;99(Suppl 3):S48–54
57. Savage DG, Lindenbaum J, Stabler SP, et al. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. Am J Med. 1994;96:239–246.
58. Bronner F. Mechanisms of intestinal calcium absorption. J Cell Biochem. 2003;88:387–393.
59. Shea B, Wells G, Cranney A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII. meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev. 2002;23:552–559
60. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354: 669–683.
61. Gilman J, Shanahan F, Cashman KD. Altered levels of biochemical indices of bone turnover and bone-related vitamins in patients with Crohn's disease and ulcerative colitis. Aliment PharmacolTher. 2006;23:1007–1016
62. Pappa HM, Grand RJ, Gordon CM. Report on the vitamin D status of adult and pediatric patients with inflammatory bowel disease and its significance for bone health and disease. Inflamm Bowel Dis. 2006;12:1162–1174
63. Siffledeen JS, Siminoski K, Steinhart H, et al. The frequency of vitamin D deficiency in adults with Crohn's disease. Can J Gastroenterol. 2003;17:473–478.
64. Sentongo TA, Semaeo EJ, Stettler N, et al. Vitamin D status in children, adolescents, and young adults with Crohn disease. Am J ClinNutr. 2002;76:1077–1081. 63. Leslie WD, Miller N, Rogal
65. Haderslev KV, Jeppesen PB, Sorensen HA, et al. Vitamin D status and measurements of markers of bone metabolism in patients with small intestinal resection. Gut. 2003;52:653–658.
66. Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. Vitamin K intake and hip fractures in women: a prospective study. Am J ClinNutr. 1999;69:74–79
67. Booth SL, Broe KE, Gagnon DR, Tucker KL, Hannan MT, McLean RR, et al. Vitamin K intake and bone mineral density in women and men. Am J ClinNutr. 2003;77:512–516.
68. Macdonald HM, McGuigan FE, Lanham-New SA, Fraser WD, Ralston SH, Reid DM. Vitamin K1 intake is associated with higher bone mineral density and reduced bone resorption in early

postmenopausal Scottish women: no evidence of genenutrient interaction with apolipoprotein E polymorphisms. Am J ClinNutr. 2008;87:1513–1520.
69. Luukinen H, Kakonen SM, Pettersson K, et al. Strong prediction of fractures among older adults by the ratio of carboxylated to total serum osteocalcin. J Bone Miner Res. 2000;15:2473–2478.
70. Szulc P, Arlot M, Chapuy MC, et al. Serum undercarboxylatedosteocalcin correlates with hip bone mineral density in elderly women. J Bone Miner Res. 1994;9:1591–1595.
71. Sinno S, Lee DS, Khachemoune A. Vitamins and cutaneous wound healing. J Wound Care. 2011;20:287–293.
72. Filippi J, Al-Jaouni R, Wiroth JB, et al. Nutritional deficiencies in patients with Crohn's disease in remission. Inflamm Bowel Dis. 2006; 12:185–191.
73. Hengstermann S, Valentini L, Schaper L, et al. Altered status of antioxidant vitamins and fatty acids in patients with inactive inflammatory bowel disease. ClinNutr. 2008;27:571–578.
74. Driscoll RH Jr, Rosenberg IH. Total par-enteral nutrition in inflammatory boweldisease. MedClin North Am1978; 62:185–201.
75. Cabré E, Domènech E. Impact of environmental and dietary factors on the course of inflammatory bowel disease. World J Gastroenterol 2012;18:3814e22.
76. Turner D, Zlotkin SH, Shah PS, Griffiths AM. Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2009;1:CD006320.
77. Turner D, Zlotkin SH, Shah PS, Griffiths AM. Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2009;1:CD006320
78. Russo I, Luciani A, De Cicco P, Troncone E, Ciacci C. Butyrate attenuates lipopolysaccharide-induced inflammation in intestinal cells and Crohn's mucosa through modulation of antioxidant defense machinery. PLoS One 2012;7: e32841
79. Kovarik JJ, Tillinger W, Hofer J, Hölzl MA, Heinzl H, Saemann MD, et al. Impaired anti-inflammatory efficacy of n-butyrate in patients with IBD. Eur J Clin Invest 2011;41:291e8.
80. Yamamoto T, Nakahigashi M, Umegae S, Matsumoto K. Enteral nutrition for the maintenance of remission in Crohn's disease: a systematic review. Eur J GastroenterolHepatol 2010;22:1e8.
81. SocietàItaliana di NutrizioneParenterale e Enterale (SINPE). LineeGuida SINPE per la nutrizioneartificialeospedaliera 2002. RivistaItaliana di NutrizioneParenterale e Enterale 2002;S5:S5e8
82. Muller C, Compher D, Druyan ME., the American Society for Parenteral and Enteral Nutrition (ASPEN). ASPEN Clinical Guidelines: nutrition screening, assessment, and intervention in adults. JPEN J Parenter Enteral Nutr 2011;35: 16e24.
83. Han PD, Burke A, Baldassano RN, Rombeau JL, Lichtenstein GR. Nutrition and inflammatory bowel disease. GastroenterolClin North Am 1999;28:423e43.
84. Borrelli O, Cordischi L, Cirulli M, Paganelli M, Labalestra V, Uccini S, et al. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. ClinGastroenterolHepatol 2006;4(7):44e53
85. Markel TA, Lou DC, Pfefferkorn M, Scherer 3rd LR, West K, Rouse T, et al. Steroids and poor nutrition are associated with infectious wound complications in children undergoing first stage procedures for ulcerative colitis. Surgery 2008;144:540e5.
86. Bannerjee K, Camacho-Hübner C, Babinska K, Dryhurst KM, Edwards R, Savage MO, et al. Anti-inflammatory and growth-stimulating effects precede nutritional restitution during enteral feeding in Crohn disease. J Pediatr GastroenterolNutr 2004;38:270e5.
87. Griffiths AM, Ohlsson A, Sherman PM, Sutherland LR. Meta-analysis of enteral nutrition as a primary treatment of active Crohn's disease. Gastroenterology 1995;108:1056e67.
88. Fernández-Banares F, Cabré E, Esteve-Comas M, Gassull MA. How effective is enteral nutrition in inducing clinical remission in active Crohn's disease? A meta-analysis of the randomized clinical trials. JPEN J Parenter Enteral Nutr 1995;19:356e64
89. Dziechciarz P, Horvath A, Shamir R, Szajewska H. Meta-analysis: enteral nutrition in active Crohn's disease in children. Aliment PharmacolTher 2007;26: 795e806.
90. Heuschkel RB, Menache CC, Megerian JT, Baird AE. Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. J PediatrGastroenterolNutr 2000;31:8e15.
91. Hanai H, Iida T, Takeuchi K, Arai H, Arai O, Abe J, et al. Nutritional therapy versus 6- mercaptopurine as maintenance therapy in patients with Crohn's disease. Dig Liver Dis 2012;44:649e54.
92. Hartman C, Eliakim R, Shamir R. Nutritional status and nutritional therapy in inflammatory bowel diseases. World J Gastroenterol 2009;15:2570e8
93. Forbes A, Goldesgeyme E, Paulon E. Nutrition in inflammatory bowel disease. JPEN J Parenter Enteral Nutr 2011..http://dx.doi.org/10.1177/0148607111413599.
94. Goh J, O'Morain A. Review article: nutrition and adult inflammatory bowel disease. Aliment PharmacolTher 2003;7:307e20
95. A.S.P.E.N. Board of Directors and the clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. J Parenter Enteral Nutr 2002;26:73SAe4SA.

96. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Longterm survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology 1999;117:1043e50.
97. Buchman AL. Complications of long-term total parenteral nutrition: their identification, prevention and treatment. Dig Dis Sci 2001;45:1e18.
98. Cabrè E, Gassull MA. Nutrition in inflammatory bowel disease: impact on disease and therapy. CurrOpinGastroenterol 2001;17:342e9.
99. Lucendo AJ, De Rezende LC. Importance of nutrition in inflammatory bowel disease. World J Gastroenterol 2009;15:2081e8.
100. Long MD, Crandall WV, Leibowitz IH, Duffy L, del Rosario F, Kim SC, et al. Prevalence and epidemiology of overweight and obesity in children with inflammatory bowel disease. Inflamm Bowel Dis 2011;17:2162e8.