Vitamins and Minerals in Inflammatory Bowel Disease

Fayez K. Ghishan, MD[a], Pawel R. Kiela, DVM, PhD[a,b,*]

KEYWORDS

• Crohn disease • Ulcerative colitis • Diet • Nutrition • Deficiency • Supplementation

KEY POINTS

- Vitamin and mineral deficiencies are common among inflammatory bowel disease (IBD) patients and warrant supplementation to restore recommended values.
- Those deficiencies likely contribute to the disease severity and associated comorbidities.
- There is a need for more evidence-based approaches supported by well-designed clinical trials to document the optimal supplementation level and to assess the benefits of supplementation exceeding the recommended daily allowance.

INTRODUCTION: FIXING DEFICIENCIES OR OVERSUPPLEMENTATION?

The role of diet in the pathogenesis of inflammatory bowel disease (IBD) remains an open topic despite the advances in the understanding of the gastrointestinal pathophysiology microbiology and mucosal immunology. A shift from a more aboriginal food to the highly refined and processed western diet, and the associated change in gut microbiome, as contributing environmental factors has been suggested by many nutritional studies.[1] The observed increased risk of autoimmune disease diagnosis among children and second-generation immigrants from regions of the world with low IBD incidence to developed countries with higher incidence of IBD also suggests the role of change in dietary habits.[2] Whereas singularly pointing to diet or dietary constituents as the main culprit that precipitates or promotes this complex disease has been very difficult, studying nutritional deficiencies, inherently associated with the course of IBD, is feasible and has been systematically done for decades.[3,4]

Complementary and alternative medicine (CAM) encompasses a vast array of treatment options, including dietary interventions. In IBD patients, they are aimed at eliminating food triggers and improving nutrition, and include supplementation of

[a] Department of Pediatrics, University of Arizona, Tucson, AZ, USA; [b] Department of Immunobiology, University of Arizona, Tucson, AZ, USA
* Corresponding author. Department of Pediatrics, University of Arizona, 1501 North Campbell Avenue, Room 6351, Tucson, AZ 85724.
E-mail address: pkiela@peds.arizona.edu

Gastroenterol Clin N Am 46 (2017) 797–808
http://dx.doi.org/10.1016/j.gtc.2017.08.011 gastro.theclinics.com

vitamins and other micronutrients and macronutrients. Nutritional interventions are an integral part of clinical practice, although evidence from clinical studies is relatively uncommon and frequently suffers from inadequate design and/or small numbers of subjects. In some instances, for example, vitamin D_3, supplementation with doses far exceeding the recommended daily allowances has been proposed.[5] Considering the size of the US supplement industry (estimated at as much as $37 billion),[6] wide general use of over-the-counter supplements, including vitamins and minerals, and high rate of CAM use among patients with gastrointestinal disorders and IBD in particular,[7] it is important to consider the efficacy of vitamin and mineral supplements, especially in the context of alleviating the primary and secondary symptoms of disease.

The mechanisms responsible for nutritional deficiencies are not always clear and could be related to decreased intake, malabsorption, or excess losses. Increased metabolic demand related to the active inflammatory process should also be taken into consideration. Micronutrient and vitamin deficiencies are relatively common among IBD patients, especially in Crohn disease (CD) with active small bowel disease, or patients undergoing intestinal resection. Those deficiencies have been subject to several excellent reviews,[3,4,8] a comprehensive recent monograph on nutritional management of IBD,[9] and are discussed relatively briefly in this article. This article briefly describes the state of knowledge regarding vitamin and mineral deficiencies, and presents and discusses the studies related to the efficacy of selected vitamin and mineral supplements in preclinical models of IBD and in clinical trials.

VITAMIN A

Serum retinol concentrations are typically used to identify vitamin A deficiency risk. Based on this factor alone, a high proportion of adult and pediatric IBD patients has been diagnosed with deficiency.[10–12] da Rocha and colleagues[13] published a case report of retinol deficiency and night blindness in a CD patient with repeated small bowel resections. Sufficiency and normal eyesight was restored by regular parenteral vitamin A administration.[13] However, serum retinol concentrations do not begin to decline until liver reserves of vitamin A are close to exhaustion, thus it is plausible that different assessment of vitamin A status that accounts for hepatic storage, would yield higher numbers of vitamin A-deficient IBD patients. Indeed, when Soares-Mota and colleagues[14] measured relative dose response in serum retinol after ingestion of retinyl palmitate as an indirect indicator of the hepatic retinol storage, a higher percentage of CD patients was diagnosed with insufficiency compared with measurement of steady-state serum level of retinol (37% vs 29%, respectively). Although no association was found between vitamin A status assessed this way with ileal disease, ileal resection, disease duration, or C-reactive protein (CRP) level, CD patients with vitamin A deficiency had significantly lower body mass index and body fat than those with normal levels.[14]

Retinoic acid, a metabolite of retinol, plays key roles in maintaining mucosal immune homeostasis by supporting the tolerogenic dendritic cells (DCs), balancing Th17 and regulatory T cell responses, gut homing of the innate lymphoid cells, and immunoglobulin-A class switching in B cells.[15] In rodent IBD models, vitamin A deficiency exacerbates inflammation, and supplementation offers protection.[16–19] Human studies with vitamin A or retinoic acid supplementation are sparse and disappointing. Wright and colleagues[20] showed no benefit of 50,000 U twice daily in a double-blind study involving 68 subjects with CD. In another small study by Norrby and

colleagues,[21] 150,000 U of vitamin A daily led to no measurable improvement in 8 subjects with severe CD.

Perhaps those failures are in part due to the pleiotropy of the effects of vitamin A and its metabolites on the mucosal immune system. Effectiveness of vitamin A supplementation may be potentially limited due to reduced expression of aldehyde dehydrogenase 1 family member (A2ALDH1a2), a pivotal enzyme in the synthesis of all-trans retinoic acid (atRA) from retinol in DCs[22] and/or increased activity of atRA-catabolizing enzyme, CYP26A1.[23–25] It is, nevertheless, prudent to supplement vitamin A in confirmed cases of deficiency to at least meet the recommended dietary allowance (RDA) of 900 μg (3000 IU) daily for adult men and 700 μg (2300 IU) daily for adult women.

VITAMIN B1 (THIAMINE)

Thiamine (mainly thiamine pyrophosphate) is indispensable for carbohydrate metabolism, mitochondrial adenosine triphosphate (ATP) production, and reduction of cellular oxidative stress. Low intracellular levels of thiamine lead to acute energy failure, propensity for oxidative stress, and mitochondrial abnormalities. Symptoms of thiamine deficiency, which may be associated with diet rich in highly refined carbohydrates (polished rice, white flour, white sugar) or during general malnutrition (eg, anorexia), range from nonspecific fatigue, irritability, poor memory, sleep disturbances, or abdominal discomfort among others, to severe neurologic deficits, such as beriberi, Wernicke encephalopathy, Korsakoff psychosis, or their combination (Wernicke-Korsakoff syndrome). Case reports have been published that include severe optic neuropathy and oculomotor palsy in UC patients that were correctable by high doses of vitamin B1,[26] and clinical and radiological diagnosis of Wernicke's encephalopathy in CD patients on parenteral nutrition.[27,28]

The role of thiamine in general energy metabolism suggested a potential role for intracellular thiamine deficiency in the pathogenesis of IBD-associated fatigue. In a pilot study with 12 subjects with CD with normal blood thiamine and thiamine pyrophosphate, Costantini and Pala[29] showed that 600 to 1,500 mg of thiamine daily completely alleviated symptoms of fatigue in 10 out of 12 subjects, with the remaining 2 also reporting significant improvement.

BIOTIN

Humans are not able to synthesize biotin (vitamin B7, also referred to as vitamin H), which must be obtained from dietary sources or bacterial synthesis by gut microbiota. Biotin functions as cofactor for 5 carboxylases critical in the fatty acid, glucose, and amino acid metabolism; cellular energy metabolism; and the regulation of cellular oxidative stress. Biotin deficiency, among other consequences, has been implicated in immune dysfunction,[30] although the effects of supplementation are not easily interpretable. Wiedmann and colleagues[31,32] showed that daily supplementation with 2150 μg of biotin for 21 days (RDA is 300 μg daily) enhanced T helper (Th)-1 and inhibited Th2 responses in restimulated peripheral blood mononuclear cells (PBMCs). This may indicate a divergent response in CD (worsening) and UC patients (improvement of symptoms) should they increase their daily intake to such levels. In vitro, biotin deficiency promoted nuclear factor-kappa beta (NF-κβ) activation and tumor necrosis factor (TNF) expression in murine macrophages,[33] and an enhanced inflammatory response was recently shown in biotin-deficient human monocyte-derived dendritic cells.[34] However, biotin deficiency has not been conclusively demonstrated in IBD, with inconsistent reports published.[35–37]

VITAMIN B6

Pyridoxal 5′-phosphate (PLP) is the biologically active form of vitamin B6 and serves as a cofactor for more than 140 biochemical reactions involved in a vast array of metabolic pathways.[38] Although severe vitamin B6 deficiency is uncommon, mild insufficiency (plasma PLP <20 nmol/L) is observed in 10% to 16% of the adult US population.[39] In mammals, food and gut commensal bacteria are the 2 main sources of vitamin B6. PLP tends to be generally reduced in patients with inflammatory conditions and is inversely correlated with CRP concentration.[40] Restoring normal levels in patients with inflammation requires higher dietary intake.[41] Saibeni and colleagues[42] showed that subjects with active CD and UC have significantly lower plasma PLP concentrations than subjects with quiescent disease or healthy controls. However, the relationship between inflammation and B6 level is not straightforward. In mice, short-term (2-week) B6 and B12 deprivation reduced the severity of dextran sodium sulphate (DSS)-induced colitis and the investigators attributed these unexpected results to B6 deficiency alone.[43] In interleukin (IL)-$10^{-/-}$ mice with chronic colitis, a bell-shaped response curve was shown; that is, reduced inflammation at both deficiency and oversupplementation as compared with a normal B6 status after 12-week dietary intervention. The investigators suggested that reduced inflammation in supplemented animals may be the result of reduced local colonic levels of sphinosine-1-phosphate (S1P), a potent chemoattractant, a phenomenon potentially related to the role of PLP as a cofactor of the S1P-metabolizing enzymes: serine C-palmitoyltransferase and S1P lyase.[44]

VITAMIN B12 AND FOLIC ACID

These 2 nutrients are especially known for their role in erythropoiesis and association with IBD-associated anemia. Vitamin B12 (cobalamin) and folate have crucial roles in nucleic acid synthesis and erythropoiesis. During their differentiation, erythroblasts require both vitamins for proliferation, and their deficiency leads to macrocytosis, erythroblast apoptosis, and anemia. Although several reports showed higher prevalence of B12 deficiency in CD than in healthy controls, a meta-analysis (3732 subjects) by Battat and colleagues[45] concluded that there is insufficient evidence in the literature to suggest an association, regardless of the ileal involvement. However, consistent with the ileum being the primary site of B12 absorption, ileal resection of greater than 30 cm in Crohn subjects were found to predispose to deficiency and warrant treatment.[45] Although similar meta-analysis of folate deficiency has not been performed, Bermejo and colleagues[46] reported that the prevalence is higher among subjects with CD (22.2%) than in subjects with UC (4.3%), and was associated with disease severity, but not ileal resection. The recent guidelines of the European Crohn's and Colitis Organisation (ECCO) recommend checking for cobalamin and folate level at least once per year or when macrocytosis is present, especially in patients not receiving thiopurines, which may directly elevate mean corpuscular volume. Although folate deficiency and elevated homocysteine have been suggested to contribute to IBD-associated colon cancer, contradicting data from preclinical studies with folic acid supplementation were published. Carrier and colleagues[47] used a complex model of UC-associated colon cancer with IL-2 and β2-microglobulin double knockout mice and showed a significantly lower incidence of high-grade lesions in the folate-supplemented group (8 mg/kg diet for 32 weeks). However, the same dose in 12-week treatment regime in DSS-azoxymethane (AOM) model of colitis-associated cancer showed no measurable effect on tumor formation or colonic microbiome composition.[48]

IRON

Iron is an essential element for blood production and is responsible for reversible oxygen binding in the hemoglobin. The incidence of iron deficiency anemia (IDA) and the associated fatigue is high in IBD patients with prevalence reported in 36% to 76% of patients.[49] The etiologic factors of IDA in IBD patients include inadequate intake, chronic blood loss caused by mucosal ulcerations, and anemia of chronic inflammation secondary to impairment of transepithelial iron absorption in the gut. The latter is associated with IL-6 driven increase in hepatic hepcidin, which binds to ferroportin on enterocytes (also monocytes and macrophages) and leads to its internalization and lysosomal degradation, thus resulting in intracellular iron sequestration.

Oral iron supplementation is the primary mode of preventing IDA secondary to blood loss or inadequate intake, with multiple and equally effective forms of iron available. Most frequently used forms are ferrous fumarate, ferrous sulfate, and ferrous gluconate, which contain 33%, 20%, and 12% of elemental iron, respectively, and are frequently combined with vitamin C to enhance absorption. For IBD patients, the Centers for Disease Control and Prevention recommends 30 mg/d of elemental iron for IDA prophylaxis, and 50 to 60 mg/d for treatment. However, oral supplementation in IBD may be ineffective in the settings of normocytic anemia of chronic inflammation. It may also be poorly tolerated with adverse effects, such as epigastric pain, nausea, flatulence, and diarrhea, which lead to poor adherence to treatment. High doses and excess of nonabsorbed iron in IBD may also be toxic to the epithelium because it undergoes Fenton reaction with hydrogen peroxide and increases inflammatory response. The efficacy of oral iron is low in patients with high levels of CRP and, in general, oral supplementation is considered safer and more effective in IBD patients with inactive or mild disease. Newer oral preparations, such as ferric maltol, a combination of iron and maltol (3-hydroxy-2-methyl-4-pyrone), offer a viable alternative to the more mainstream forms of iron in mild-to-moderate IBD without resorting to intravenous therapy, even in patients who do not tolerate oral ferrous products.[50] However, ferric maltol is not yet available as an over-the-counter supplement. Intravenous iron infusions offer another alternative in which oral preparations are ineffective or are poorly tolerated. Because free iron is toxic, all intravenous iron contains carbohydrates that bind the elemental iron to prevent reactions. ECCO guidelines recommend intravenous iron to be considered the first line of treatment in patients with clinically active IBD, previous intolerance to oral iron, hemoglobin lower than 10 g/dL, or in patients with documented need for erythropoiesis-stimulating agents.[51]

VITAMIN D_3 AND CALCIUM

Vitamin D is an essential nutrient with wide systemic effects. Regulation of the innate and adaptive immune responses and regulation of calcium homeostasis and bone metabolism are of particular importance in IBD due to immune dysregulation and inflammation-associated loss of bone mineral density prevalent among IBD patients. Vitamin D3 (cholecalciferol) is the natural form of vitamin D active in humans and is provided in diet and synthesized in the skin via UV-B exposure and thermal conversion. After 2 hydroxylation steps in the liver and kidney, $1,25(OH)_2$ D_3 becomes the most biologically active form of D_3. Clinically measured $25(OH)D_3$ is considered a better marker of dietary intake or absorption, hepatic stores and conversion, and general systemic availability. Although the guidelines are somewhat fluid, blood levels of $25(OH)D_3$ less than 20 ng/mL are considered as a deficiency, with 30 to 100 ng/mL considered optimal. Concentrations of greater than or equal to 150 ng/mL have been associated with toxicity. Among all nutritional deficiencies in IBD, vitamin D_3

received the most attention with relatively consistent reports of prevalent deficiency or insufficiency.[52,53] Vitamin D_3 deficiency is considered to be an etiologic factor behind impaired epithelial calcium absorption and bone metabolism,[54] as well as potential defects in the function of innate immune system (eg, phagocyte bacterial killing) and dysregulation of the adaptive immune responses.[55]

Restoring normal levels is imperative in clinical care and has been associated with beneficial clinical outcomes.[56,57] Both vitamin D_2 (ergocalciferol) and D_3 (cholecalciferol) are available and used as supplements, although the overall biological activity of ergocalciferol was estimated to be no more than 30% of cholecalciferol. Thus, cholecalciferol or natural sources of vitamin D_3 (especially oily fish like salmon, mackerel, herring, and cod liver) are the preferred forms of supplementation. Current vitamin D intake recommendations of the Institute of Medicine suggest 1000 to 2000 IU/d in healthy adults, a dose embraced by the Endocrine Society's Clinical Practice Guidelines, which also considered 10,000 IU/d to be safe. Although there are no strict developed guidelines for IBD patients, an annual screening of $25(OH)D_3$ is recommended, especially in patients on steroid therapy. Supplementation of 600 IU/d and 800 IU/d has been considered adequate in patients with normal D_3 levels who are between 1 and 70 years old, and greater than 70 years, respectively. In adults at risk for deficiency (in the insufficiency range), a daily intake of 1000 IU/d is recommended and 6000 IU/d or 50,000 IU once a week in patient with identified deficiency has been proposed. These values were developed largely with normalizing the serum levels of $25(OH)D_3$ as a primary outcome measure. The effectiveness of D_3 supplementation on bone health and inflammation in IBD is not uniformly beneficial in clinical studies. For example, the effects of vitamin D_3 alone or in combination with calcium and bisphosphonates on bone mineral density in IBD patients yielded inconclusive data, ranging from significant[58] or limited benefits.[59] In pediatric IBD patients conflicting data have been reported.[60,61] More systematic studies in pediatric and adult IBD patients need to be conducted to identify factors determining the clinical response to vitamin D and Ca^{2+} supplementation, the form and route of administered vitamin D, with careful monitoring of the parameters of bone mass, bone turnover, and mineral homeostasis. The need for such systematic approach is further justified by identification of at least a subset of IBD patients with inappropriate hypercalcitriolemia, which is elevated serum $1,25(OH)_2D_3$.[62,63] The authors' group has suggested that because cytokines associated with active inflammation, such as IL-1β, IL-6, and TNFα, may act synergistically with vitamin D_3 to negatively regulate bone turnover, high-dose vitamin D_3 supplementation in active IBD may not improve bone density or even lead to a paradoxic bone mineral density (BMD) loss[64] and that in patients at clear risk of osteopenia or osteoporosis or with proven osteopenia or osteoporosis, vitamin D_3 be withheld until remission is achieved.[54,65] This would also be consistent with vitamin D_3 supplementation as a means of relapse prevention, which has clinical support in published studies.[66,67] Although long-term high-dose D_3 supplementation has been shown in some studies to significantly reduce disease score in active IBD (eg, Yang and colleagues[68]), the effects on the bone are typically not assessed in those inflammation-centric studies.

VITAMIN K

Vitamin K is a group of structurally related fat-soluble compounds. Vitamin K_1, also known as phylloquinone, is particularly abundant in green leafy vegetables due to its involvement in photosynthesis. Both animals and their gut bacteria convert vitamin K_1 into K_2 isoforms known as menaquinones. Menaquinones differ in length from

1 to 14 repeats of 5-carbon units in the isoprenoid side chain of the molecules, are designated as MK2 though MK14, and differ in their apparent biological effects. Three synthetic types of vitamin K are known: vitamins K_3, K_4, and K_5

Vitamin K is the essential cofactor in the process of carboxylation of glutamic acid residues in many vitamin K–dependent proteins involved in blood coagulation, bone metabolism, prevention of vascular mineralization, and regulation of many other cellular functions. Early and limited study by Krasinski and colleagues[69] showed relatively high prevalence of vitamin K deficiency in CD and UC, but not celiac patients, without an identified bleeding disorder.

Bone formation by osteoblasts requires vitamin K–dependent post-translational gamma-carboxylation of glutamate residues on osteocalcin, matrix Gla protein, and protein S, whereas bone resorption is inhibited by vitamin K via inhibition of the synthesis of prostaglandin E2 by osteoclast. Consistent with the effects of vitamin K on bone metabolism, several clinical studies suggested that in CD patients, vitamin K deficiency contributes to low BMD.[70–72] However, a more recent clinical study in CD patients with vitamin K insufficiency supplemented with 1000 μg of phylloquinone (K_1) daily for 12 months (along with calcium and vitamin D_3) failed to demonstrate measurable effects on bone metabolism. It is plausible that conversion of K_1 to potentially more efficacious menaquinones (K_2) by the inflamed host and gut microbiome is altered. Although other forms, such as menatetrenone (MK)-4, have been shown to be effective in postmenopausal bone loss, they have not yet been tested in IBD patients. Interestingly, MK-4 has been shown to reduce the symptoms of DSS-induced colitis in mice, suggesting that it may also work as an immune modulator.[73]

ZINC

Zinc is an essential mineral that plays pivotal roles in many aspects of cellular metabolism, such as supporting catalytic activity of approximately 100 enzymes, modulation of immune function, protein synthesis, wound healing, DNA synthesis, cell division, and improvement of intestinal barrier function. Assessment of zinc status in patients is not straightforward because it lacks storage mechanisms and significantly fluctuates with intake. With that in mind, it has been estimated that 15% of IBD patients are affected by zinc deficiency.[74] A recent study showed that zinc deficiency in patients with CD and UC was associated with poor clinical outcomes: increased risk of subsequent hospitalizations, surgeries, and disease-related complications.[75] The investigators showed that these outcomes improve with normalization of zinc, and suggested close monitoring and replacement of zinc in IBD patients as needed. Current RDA is 11 mg/d and 8 mg/d of elemental zinc for male patients and female patients, respectively, but higher doses have been recommended or used in IBD: from 40 mg/d for 10 days to 110 mg 3 times a day for 8 weeks in CD patients in remission.[76] Chronic IBD-associated diarrhea is an additional indication for zinc supplementation. High-dose and long-tern supplementation with zinc should be used with caution, however. The upper limit (highest daily intake above which side effects or toxicity may occur) for this mineral is set to 40 mg/d, and zinc can interfere with iron and copper absorption, exacerbating their potential deficiencies. In turn, supplementation with calcium or folate and can reduce zinc absorption. Two most common supplemental forms zinc sulfate (23% of elemental zinc) and zinc gluconate (13% elemental zinc).

SUMMARY

Insufficient intake, impaired absorption via inflamed or otherwise functionally impaired epithelia, and increased metabolic needs all contribute to vitamin and mineral

deficiencies, which are relatively common among IBD patients. Although good clinical practice should include surveillance for micronutrient deficiencies and, in respective cases, a relevant treatment and supplementation, in many cases, doses needed to restore normal levels are not consistent with nutritional recommendations for healthy individuals. Better evidence-based guidelines are required to established appropriate doses. In some cases, pharmacologic doses, regardless of the confirmed deficiency, may offer benefits, although more clinical evidence to support these approaches is still needed.

REFERENCES

1. Dolan KT, Chang EB. Diet, gut microbes, and the pathogenesis of inflammatory bowel diseases. Mol Nutr Food Res 2017;61(1).
2. Benchimol EI, Mack DR, Guttmann A, et al. Inflammatory bowel disease in immigrants to Canada and their children: a population-based cohort study. Am J Gastroenterol 2015;110(4):553–63.
3. Weisshof R, Chermesh I. Micronutrient deficiencies in inflammatory bowel disease. Curr Opin Clin Nutr Metab Care 2015;18(6):576–81.
4. Massironi S, Rossi RE, Cavalcoli FA, et al. Nutritional deficiencies in inflammatory bowel disease: therapeutic approaches. Clin Nutr 2013;32(6):904–10.
5. Hlavaty T, Krajcovicova A, Payer J. Vitamin D therapy in inflammatory bowel diseases: who, in what form, and how much? J Crohns Colitis 2015;9(2):198–209.
6. Bradley J. NBJ: 'The US supplement industry is $37 billion, not $12 billion. 2015; Available at: http://www.nutraingredients-usa.com/Markets/NBJ-The-US-supplement-industry-is-37-billion-not-12-billion. Accessed March 27,2017.
7. Rossi RE, Whyand T, Murray CD, et al. The role of dietary supplements in inflammatory bowel disease: a systematic review. Eur J Gastroenterol Hepatol 2016;28(12):1357–64.
8. Hwang C, Ross V, Mahadevan U. Micronutrient deficiencies in inflammatory bowel disease: from A to zinc. Inflamm Bowel Dis 2012;18(10):1961–81.
9. Ashwin N. Ananthakrishnan, editor. Nutritional management of inflammatory bowel diseases: a comprehensive guide. New York: Springer Science+Business Media; 2016.
10. Hashemi J, Asadi J, Amiriani T, et al. Serum vitamins A and E deficiencies in patients with inflammatory bowel disease. Saudi Med J 2013;34(4):432–4.
11. Alkhouri RH, Hashmi H, Baker RD, et al. Vitamin and mineral status in patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2013;56(1):89–92.
12. Main AN, Mills PR, Russell RI, et al. Vitamin A deficiency in Crohn's disease. Gut 1983;24(12):1169–75.
13. da Rocha Lima B, Pichi F, Lowder CY. Night blindness and Crohn's disease. Int Ophthalmol 2014;34(5):1141–4.
14. Soares-Mota M, Silva TA, Gomes LM, et al. High prevalence of vitamin A deficiency in Crohn's disease patients according to serum retinol levels and the relative dose-response test. World J Gastroenterol 2015;21(5):1614–20.
15. Erkelens MN, Mebius RE. Retinoic acid and immune homeostasis: a balancing act. Trends Immunol 2017;38(3):168–80.
16. Reifen R, Nur T, Ghebermeskel K, et al. Vitamin A deficiency exacerbates inflammation in a rat model of colitis through activation of nuclear factor-kappa B and collagen formation. J Nutr 2002;132(9):2743–7.

17. Okayasu I, Hana K, Nemoto N, et al. Vitamin A inhibits development of dextran sulfate sodium-induced colitis and colon cancer in a mouse model. Biomed Res Int 2016;2016:4874809.
18. Kang SG, Wang C, Matsumoto S, et al. High and low vitamin A therapies induce distinct FoxP3+ T-cell subsets and effectively control intestinal inflammation. Gastroenterology 2009;137(4):1391–402.e1–6.
19. Collins CB, Aherne CM, Kominsky D, et al. Retinoic acid attenuates ileitis by restoring the balance between T-helper 17 and T regulatory cells. Gastroenterology 2011;141(5):1821–31.
20. Wright JP, Mee AS, Parfitt A, et al. Vitamin A therapy in patients with Crohn's disease. Gastroenterology 1985;88(2):512–4.
21. Norrby S, Sjodahl R, Tagesson C. Ineffectiveness of vitamin A therapy in severe Crohn's disease. Acta Chir Scand 1985;151(5):465–8.
22. Laffont S, Siddiqui KR, Powrie F. Intestinal inflammation abrogates the tolerogenic properties of MLN CD103+ dendritic cells. Eur J Immunol 2010;40(7):1877–83.
23. Bhattacharya N, Yuan R, Prestwood TR, et al. Normalizing microbiota-induced retinoic acid deficiency stimulates protective cd8(+) t cell-mediated immunity in colorectal cancer. Immunity 2016;45(3):641–55.
24. Sanders TJ, McCarthy NE, Giles EM, et al. Increased production of retinoic acid by intestinal macrophages contributes to their inflammatory phenotype in patients with Crohn's disease. Gastroenterology 2014;146(5):1278–88.e1-2.
25. DePaolo RW, Abadie V, Tang F, et al. Co-adjuvant effects of retinoic acid and IL-15 induce inflammatory immunity to dietary antigens. Nature 2011;471(7337):220–4.
26. van Noort BA, Bos PJ, Klopping C, et al. Optic neuropathy from thiamine deficiency in a patient with ulcerative colitis. Doc Ophthalmol 1987;67(1–2):45–51.
27. Shin IS, Seok H, Eun YH, et al. Wernicke's encephalopathy after total parenteral nutrition in patients with Crohn's disease. Intest Res 2016;14(2):191–6.
28. Zeljko K, Darija VB, Dina LK, et al. Wernicke's encephalopathy during parenteral nutrition in a Crohn's disease patient. Nutrition 2011;27(4):503–4.
29. Costantini A, Pala MI. Thiamine and fatigue in inflammatory bowel diseases: an open-label pilot study. J Altern Complement Med 2013;19(8):704–8.
30. Kuroishi T. Regulation of immunological and inflammatory functions by biotin. Can J Physiol Pharmacol 2015;93(12):1091–6.
31. Wiedmann S, Eudy JD, Zempleni J. Biotin supplementation increases expression of genes encoding interferon-gamma, interleukin-1beta, and 3-methylcrotonyl-CoA carboxylase, and decreases expression of the gene encoding interleukin-4 in human peripheral blood mononuclear cells. J Nutr 2003;133(3):716–9.
32. Wiedmann S, Rodriguez-Melendez R, Ortega-Cuellar D, et al. Clusters of biotin-responsive genes in human peripheral blood mononuclear cells. J Nutr Biochem 2004;15(7):433–9.
33. Kuroishi T, Endo Y, Muramoto K, et al. Biotin deficiency up-regulates TNF-alpha production in murine macrophages. J Leukoc Biol 2008;83(4):912–20.
34. Agrawal S, Agrawal A, Said HM. Biotin deficiency enhances the inflammatory response of human dendritic cells. Am J Physiol Cell Physiol 2016;311(3):C386–91.
35. Matsusue S, Kashihara S, Takeda H, et al. Biotin deficiency during total parenteral nutrition: its clinical manifestation and plasma nonesterified fatty acid level. JPEN J Parenter Enteral Nutr 1985;9(6):760–3.
36. Fernandez-Banares F, Abad-Lacruz A, Xiol X, et al. Vitamin status in patients with inflammatory bowel disease. Am J Gastroenterol 1989;84(7):744–8.

37. Kuroki F, Iida M, Tominaga M, et al. Multiple vitamin status in Crohn's disease. Correlation with disease activity. Dig Dis Sci 1993;38(9):1614–8.
38. Mooney S, Leuendorf JE, Hendrickson C, et al. Vitamin B6: a long known compound of surprising complexity. Molecules 2009;14(1):329–51.
39. Prevention CfDCa. Second national report on biochemical indicators of diet and nutrition in the U.S. population. 2012. Available at: https://www.cdc.gov/nutritionreport/index.html. Accessed March 27, 2017.
40. Friso S, Jacques PF, Wilson PW, et al. Low circulating vitamin B(6) is associated with elevation of the inflammation marker C-reactive protein independently of plasma homocysteine levels. Circulation 2001;103(23):2788–91.
41. Morris MS, Sakakeeny L, Jacques PF, et al. Vitamin B-6 intake is inversely related to, and the requirement is affected by, inflammation status. J Nutr 2010;140(1):103–10.
42. Saibeni S, Cattaneo M, Vecchi M, et al. Low vitamin B(6) plasma levels, a risk factor for thrombosis, in inflammatory bowel disease: role of inflammation and correlation with acute phase reactants. Am J Gastroenterol 2003;98(1):112–7.
43. Benight NM, Stoll B, Chacko S, et al. B-vitamin deficiency is protective against DSS-induced colitis in mice. Am J Physiol Gastrointest Liver Physiol 2011;301(2):G249–59.
44. Selhub J, Byun A, Liu Z, et al. Dietary vitamin B6 intake modulates colonic inflammation in the IL10-/- model of inflammatory bowel disease. J Nutr Biochem 2013;24(12):2138–43.
45. Battat R, Kopylov U, Szilagyi A, et al. Vitamin B12 deficiency in inflammatory bowel disease: prevalence, risk factors, evaluation, and management. Inflamm Bowel Dis 2014;20(6):1120–8.
46. Bermejo F, Algaba A, Guerra I, et al. Should we monitor vitamin B12 and folate levels in Crohn's disease patients? Scand J Gastroenterol 2013;48(11):1272–7.
47. Carrier J, Medline A, Sohn KJ, et al. Effects of dietary folate on ulcerative colitis-associated colorectal carcinogenesis in the interleukin 2- and beta(2)-microglobulin-deficient mice. Cancer Epidemiol Biomarkers Prev 2003;12(11 Pt 1):1262–7.
48. MacFarlane AJ, Behan NA, Matias FM, et al. Dietary folate does not significantly affect the intestinal microbiome, inflammation or tumorigenesis in azoxymethane-dextran sodium sulphate-treated mice. Br J Nutr 2013;109(4):630–8.
49. Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. Nat Rev Gastroenterol Hepatol 2010;7(11):599–610.
50. Stallmach A, Buning C. Ferric maltol (ST10): a novel oral iron supplement for the treatment of iron deficiency anemia in inflammatory bowel disease. Expert Opin Pharmacother 2015;16(18):2859–67.
51. Dignass AU, Gasche C, Bettenworth D, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis 2015;9(3):211–22.
52. Del Pinto R, Pietropaoli D, Chandar AK, et al. Association between inflammatory bowel disease and vitamin D deficiency: a systematic review and meta-analysis. Inflamm Bowel Dis 2015;21(11):2708–17.
53. Sadeghian M, Saneei P, Siassi F, et al. Vitamin D status in relation to Crohn's disease: meta-analysis of observational studies. Nutrition 2016;32(5):505–14.
54. Ghishan FK, Kiela PR. Advances in the understanding of mineral and bone metabolism in inflammatory bowel diseases. Am J Physiol Gastrointest Liver Physiol 2011;300(2):G191–201.

55. Hewison M. Vitamin D and immune function: an overview. Proc Nutr Soc 2012; 71(1):50–61.
56. Ananthakrishnan AN, Cagan A, Gainer VS, et al. Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. Inflamm Bowel Dis 2013;19(9):1921–7.
57. Ananthakrishnan AN, Khalili H, Higuchi LM, et al. Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. Gastroenterology 2012; 142(3):482–9.
58. Vogelsang H, Ferenci P, Resch H, et al. Prevention of bone mineral loss in patients with Crohn's disease by long-term oral vitamin D supplementation. Eur J Gastroenterol Hepatol 1995;7(7):609–14.
59. Bartram SA, Peaston RT, Rawlings DJ, et al. A randomized controlled trial of calcium with vitamin D, alone or in combination with intravenous pamidronate, for the treatment of low bone mineral density associated with Crohn's disease. Aliment Pharmacol Ther 2003;18(11–12):1121–7.
60. Benchimol EI, Ward LM, Gallagher JC, et al. Effect of calcium and vitamin D supplementation on bone mineral density in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2007;45(5):538–45.
61. Hradsky O, Soucek O, Maratova K, et al. Supplementation with 2000 IU of cholecalciferol is associated with improvement of trabecular bone mineral density and muscle power in pediatric patients with IBD. Inflamm Bowel Dis 2017;23(4): 514–23.
62. Abreu MT, Kantorovich V, Vasiliauskas EA, et al. Measurement of vitamin D levels in inflammatory bowel disease patients reveals a subset of Crohn's disease patients with elevated 1,25-dihydroxyvitamin D and low bone mineral density. Gut 2004;53(8):1129–36.
63. Rudnicki M, Frolich A, Transbol I. Inappropriate hypercalcitriolemia in ileum-resected patients with Crohn's disease. Miner Electrolyte Metab 1992;18(1):52–5.
64. Larmonier CB, McFadden RM, Hill FM, et al. High vitamin D3 diet administered during active colitis negatively affects bone metabolism in an adoptive T cell transfer model. Am J Physiol Gastrointest Liver Physiol 2013;305(1):G35–46.
65. Kiela PR, Ghishan FK. Metabolic bone disease in patients with inflammatory bowel disease. Pract Gastroenterol 2012;XXXVI(9):16–26.
66. Jorgensen SP, Agnholt J, Glerup H, et al. Clinical trial: vitamin D3 treatment in Crohn's disease - a randomized double-blind placebo-controlled study. Aliment Pharmacol Ther 2010;32(3):377–83.
67. Miheller P, Muzes G, Hritz I, et al. Comparison of the effects of 1,25 dihydroxyvitamin D and 25 hydroxyvitamin D on bone pathology and disease activity in Crohn's disease patients. Inflamm Bowel Dis 2009;15(11):1656–62.
68. Yang L, Weaver V, Smith JP, et al. Therapeutic effect of vitamin d supplementation in a pilot study of Crohn's patients. Clin Transl Gastroenterol 2013;4:e33.
69. Krasinski SD, Russell RM, Furie BC, et al. The prevalence of vitamin K deficiency in chronic gastrointestinal disorders. Am J Clin Nutr 1985;41(3):639–43.
70. Schoon EJ, Muller MC, Vermeer C, et al. Low serum and bone vitamin K status in patients with longstanding Crohn's disease: another pathogenetic factor of osteoporosis in Crohn's disease? Gut 2001;48(4):473–7.
71. Duggan P, O'Brien M, Kiely M, et al. Vitamin K status in patients with Crohn's disease and relationship to bone turnover. Am J Gastroenterol 2004;99(11):2178–85.
72. Nowak JK, Grzybowska-Chlebowczyk U, Landowski P, et al. Prevalence and correlates of vitamin K deficiency in children with inflammatory bowel disease. Sci Rep 2014;4:4768.

73. Shiraishi E, Iijima H, Shinzaki S, et al. Vitamin K deficiency leads to exacerbation of murine dextran sulfate sodium-induced colitis. J Gastroenterol 2016;51(4):346–56.
74. Vagianos K, Bector S, McConnell J, et al. Nutrition assessment of patients with inflammatory bowel disease. JPEN J Parenter Enteral Nutr 2007;31(4):311–9.
75. Siva S, Rubin DT, Gulotta G, et al. Zinc deficiency is associated with poor clinical outcomes in patients with inflammatory bowel disease. Inflamm Bowel Dis 2017;23(1):152–7.
76. Sturniolo GC, Di Leo V, Ferronato A, et al. Zinc supplementation tightens "leaky gut" in Crohn's disease. Inflamm Bowel Dis 2001;7(2):94–8.