Vitamins and minerals in IBD

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Summary

While indiscriminate use of multivitamins and mineral supplements in the general population is increasingly scrutinized as largely useless and sometimes potentially harmful, populations at risk of nutritional deficiencies, such as patients with chronic Inflammatory Bowel Diseases (IBD), need to be monitored and compensated for nutritional and metabolic losses. Clear mechanistic links between vitamin and mineral deficiencies and the associated IBD pathology has been found for some nutrients and normalizing their systemic level has proven clinically beneficial. Others, like vitamin A, although instinctively desirable, resulted in disappointing results. In some cases, restoring normal levels of the selected vitamins and minerals requires elevated doses to compensate for defects in absorptive mechanisms or signaling pathways negatively affected by the inflammatory process. In this review, we describe some aspects of vitamin and mineral deficiencies among IBD patients, and in the absence of clear clinical guidelines, we summarize pros and cons of supplementation frequently considered to be an element of the complementary and alternative medicine.

Keywords

Crohn's disease; Ulcerative colitis; Diet; Nutrition; Deficiency; Supplementation

Introduction: fixing deficiencies or over-supplementation?

The role of diet in the pathogenesis of Inflammatory Bowel Diseases (IBD) remains an open topic despite the advances in our understanding of the gastrointestinal (patho)physiology 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

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countries with higher incidence of IBD also suggests the role of change in dietary habits.[2] While singularly pointing to diet or dietary constituent(s) 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 vitamins and other micro- 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 patients. In some instances, e.g. 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 to as much as $37 billion)[6], wide general use of over the counter supplements, including vitamins and minerals, and high rate of CAM utilization 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's Disease 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 will only be discussed relatively briefly in this review. We will briefly describe the state of knowledge regrading vitamin and mineral deficiencies, and present and discuss 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 is 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 et al.[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 et al.[14] measured relative dose response (RDR) in serum retinol after ingestion of retinyl palmitate as an indirect indicator of the hepatic retinol storage, higher percentage of CD patients were diagnosed with insufficiency compared to 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 CRP level, CD patients with vitamin A deficiency had significantly lower BMI 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 (DC), balancing Th17 and regulatory T cell (Treg) responses, gut homing of the innate lymphoid cells (ILC), and IgA 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 et al.[20] showed no benefit of 50,000 U twice daily in a double blind study involving 68 CD patients. In another small study by Norrby et al.,[21] 150,000 U of vitamin A daily led to no measurable improvement in 8 patients 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 ALDH1a2 (Aldehyde Dehydrogenase 1 Family Member A2), a pivotal enzyme in the synthesis of all-trans retinoic acid (atRA) from retinol in DC's [22] and/or increased activity of atRA-catabolizing enzyme, CYP26A1.[23] It is nevertheless prudent to supplement vitamin A in confirmed cases of deficiency, to at least meet the recommended dietary allowance (RDA) of 900μg (3,000 IU) daily for adult men and 700μg (2,300 IU) daily for adult women.

Vitamin B1 (thiamine)

Thiamine (mainly thiamine pyrophosphate), is indispensable for carbohydrate metabolism, mitochondrial 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 (e.g. anorexia), range from non-specific 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, which include severe optic neuropathy and oculomotor palsy in UC patient 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 CD patients with normal blood thiamine and thiamine pyrophosphate, Constantini and Pala[29] showed that 600–1,500mg of thiamine daily completely alleviated symptoms of fatigue in 10 out of 12 patients, with the remaining two 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 five 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 et al.[31, 32] showed that daily supplementation with 2,150 μg of biotin for 21 days (RDA is at 300 μg daily) enhanced Th1 and inhibited Th2 responses in restimulated PBMC's. 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 NF-kB activation and 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, is a cofactor for over 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 10–16% of the adult US population.[39] In mammals, food and gut commensal bacteria are the two main sources of vitamin B6. PLP tends to be generally reduced in patients with inflammatory conditions and is inversely correlated with C-reactive protein (CRP) concentration.[40] Restoring normal levels in patients with inflammation requires higher dietary intake.[41] Saibeni et al.[42] showed that patients with active CD and UC have significantly lower plasma PLP concentrations than patients with quiescent disease or healthy controls. However, the relationship between inflammation and B6 level is not straightforward. In mice, short-term (two-week) B6 and B12 deprivation reduced the severity of DSS-induced colitis and the authors attributed these unexpected results to B6 deficiency alone.[43] In IL-10$^{-/-}$ mice with chronic colitis, a bell-shaped response curve was shown, i.e. reduced inflammation at both deficiency and over-supplementation as compared to a normal B6 status after 12-week dietary intervention. The authors 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 co-factor of S1P-metabolizing enzymes, serine C-palmytoyltransferase and S1P lyase.[44]

Vitamin B12 and folic acid

These two 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 Crohn's disease than in healthy controls, a meta-analysis (3,732 patients) by Battat et al.[46] 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 >30 cm in Crohn's patients were found to predispose to deficiency and warrant treatment.[46] Although similar meta-analysis of folate deficiency has not been performed, Bormejo et al.[47] reported that the prevalence is higher among CD (22.2%) than in UC patients (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 (MCV). 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 et al.[48] 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 (8mg/kg diet for 32 weeks). However, the same dose in 12-week treatment regime in DSS/AOM model of colitis-associated cancer showed no measurable effect on tumor formation or colonic microbiome composition.[49]

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 36–76% of patients.[50] The etiology of IDA in IBD patients includes 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/day of elemental iron for IDA prophylaxis, and 50–60 mg/day 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 non-absorbed iron in IBD may also be toxic to the epithelium as it undergoes Fenton reaction with hydrogen peroxide, and increases inflammatory response. The efficacy of oral iron is low in patients with high levels of C-reactive protein (CRP), and in general, oral supplementation is considered safer and more effective in IBD patients with inactive or mild disease. Newer oral preparation 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.[51] However, ferric maltol is not yet available as an over-the-counter supplement. Intravenous iron infusions offer another alternative where 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 below 10 g/dl or in patients with documented need for erythropoiesis-stimulating agents.[52]

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 UVB exposure and thermal conversion. After two 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/absorption, hepatic stores and conversion, and general systemic availability. While the guidelines are somewhat fluid, blood levels of $25(OH)D_3$ <20ng/mL are considered as deficiency, with 30–100ng/mL considered optimal. Concentrations of 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.[53, 54] Vitamin D_3 deficiency is considered to be one of the etiological factors behind impaired epithelial calcium absorption and bone metabolism[55], as well as potential defects in the function of innate immune system (e.g. phagocyte bacterial killing) and dysregulation of the adaptive immune responses.[56]

Restoring normal levels is imperative in clinical care, and has been associated with beneficial clinical outcomes.[57, 58] 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 1,000–2,000 IU/day in healthy adults, a dose embraced by the Endocrine Society's Clinical Practice Guidelines, which also considered 10,000 IU/day 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/day and 800 IU/day has been considered adequate in patients with normal D_3 levels in 1–70 years old bracket and >70 years, respectively. In adults at risk for deficiency (in the insufficiency range), a daily intake of 1,000 IU/day is recommended and 6,000 IU/day 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 primary outcome measure. The effectiveness

of D_3 supplementation on bone health and inflammation in IBD is not uniformly beneficial in clinical studies. As an 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[59] or limited benefits.[60] In pediatric IBD patitents conflicting data have been reported.[61, 62] 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 (elevated serum $1,25(OH)_2D_3$).[63, 64] Our group has been suggested that since 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 paradoxical BMD loss[65] 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.[55, 66] This would also be consistent with vitamin D_3 supplementation as means of relapse prevention, which has clinical support in published studies.[67, 68] Although long-term high-dose D_3 supplementation has been shown in some studies to significantly reduce disease score in active IBD (e.g. Yang et al.[69]) 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 K_1 into vitamin K_2 isoforms known as menaquinons. Menaquinones differ in length from 1 to 14 repeats of 5-carbon units in the isoprenoid side chain of the molecules and 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 Krasinsky et al.[70] 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 gammacarboxylation of glutamate residues on osteocalcin, matrix Gla protein, and protein S, while 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. [71,72, 73] However, a more recent clinical study in CD patients with vitamin K insufficiency supplemented with 1,000 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

menaquinons (K_2) by the "inflamed" host and gut microbiome is altered. Although other forms like menatetrenone (MK-4) have been shown to be effective in post-menopausal 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.[74]

Zinc

Zinc is an essential mineral that plays pivotal roles in many aspects of cellular metabolism, such as supporting catalytic activity of approx. 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, as 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.[80] A recent study showed that zinc deficiency in CD and UC patients was associated with poor clinical outcomes: increased risk of subsequent hospitalizations, surgeries, and disease-related complications.[81] The authors 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 11mg/day and 8mg/day of elemental zinc for males and females, respectively, but higher doses have been recommended or used in IBD, from 40 mg/day for 10 days to 110 mg three times a day for 8 weeks in CD patients in remission[82] 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. Upper limit (UL; highest daily intake above which side effects/toxicity may occur) for this mineral is set to 40 mg/day and zinc can interfere with iron and copper absorption and exacerbate their potential deficiencies. In turn, supplementation with calcium or folate and can reduce Zn absorption. Two most common supplemental forms zinc sulfate (23% of elemental Zn) and zinc gluconate (13% elemental Zn).

Summary

Insufficient intake, impaired absorption via inflamed or otherwise functionally impaired epithelia, 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, pharmacological doses regardless of the confirmed deficiency, may offer benefits, although more clinical evidence to support these approaches is still needed.

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Key Points

- Vitamin and mineral deficiencies are common among IBD patients and warrant supplementation to restore recommended values.

- Those deficiencies likely contribute to the disease severity and associated co-morbidities.

- 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.