Micronutrient deficiencies in inflammatory bowel disease

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Purpose of review
Malnutrition, protein-energy, and micronutrient deficiencies are common among patients with inflammatory bowel disease (IBD). The deficiencies are a manifestation of the complicated disease and a cause of morbidity. The present review summarizes recent advances and evidence-based knowledge regarding micronutrients in relation to patients with IBD.

Recent findings
Micronutrient deficiencies occur in more than half of patients with IBD. Most common are deficiencies of iron, B12, vitamin D, vitamin K, folic acid, selenium, zinc, vitamin B6, and vitamin B1. Deficiencies are more common in Crohn's disease than in ulcerative colitis, and more in active disease than at times of remission. Micronutrient deficiency is associated with prolonged and complicated course of disease. Iron deficiency is the most common cause for anemia. Definite diagnosis of B12 deficiency cannot be established by serum levels alone. Vitamin D and vitamin K deficiencies are thought to be associated with heightened inflammatory state. The relationship of these deficiencies with bone disease is controversial. The present review focuses on the significance, epidemiology, treatment options, and recommendations regarding micronutrient deficiencies in IBD.

Summary
Micronutrient deficiencies are common and have clinical significance. High suspicion for micronutrient deficiencies is advocated so that treatable causes of morbidity are treated appropriately and late and irreversible sequlae are prevented.

Keywords
inflammatory bowel disease, malnutrition, micronutrients

INTRODUCTION

The present review focuses on micronutrient deficiencies in ulcerative colitis and Crohn's disease. Malnutrition is present in up to 85% of patients with inflammatory bowel disease (IBD), both in the active stage of the disease and when it is in remission. Overall, the prevalence of malnutrition in patients with ulcerative colitis is lower than in patients with Crohn's disease [1], and in quiescent versus active disease. Malnutrition in patients with IBD is multifactorial. Reasons include impaired dietary intake, impaired absorption, direct loss, or increased energy expenditure not coupled with increased intake. Impaired intake can be the result of multiple factors such as anorexia, abdominal pain, nausea, patient preferences, the influence of medications, or recommendations of the medical staff.

Nutritional deficiencies carry a significant risk of poor outcome. Patients with IBD with malnutrition are prone to prolonged hospitalization [2,3], a complicated peri-operative course [4], and higher mortality [2] than are patients with IBD who are not malnourished. Disease-related malnutrition (DRM) can include protein-calorie, micronutrients deficiency, or both. The most frequent micronutrients that are deficient in patients with IBD are B12, folate, iron, and Vitamin D. Micronutrient deficiencies can present different clinical manifestations in the chronic and acute settings. Malnutrition is associated with adverse effects of treatment, for example, low cholesterol levels, cyclosporin treatment is associated with central

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KEY POINTS

- Iron, B12, vitamin D, vitamin K, folic acid, selenium, zinc, vitamin B6, and vitamin B1 deficiencies are common in patients with IBD.
- Iron deficiency is the leading cause of anemia in patients with IBD, and usually correlates with disease activity. The threshold for treatment, route (parenteral or oral), and dosage depend on level of deficiency, symptomatology, level of hemoglobin, and disease activity.
- Vitamin K and vitamin D deficiencies correlate with disease activity. Their role in metabolic bone disease is questionable. There is evidence regarding their role in inflammation.
- Definite diagnosis of vitamin B12 deficiency necessitates functional studies such as low homocysteine or high methylmalonilic acid levels. The only risk factor for B12 deficiency is ileal resection of more than 30 cm; otherwise, the prevalence of deficiency is equivalent to that of the general population.

nervous system (CNS) complications, and hypomagnesemia is associated with cyclosporin toxicity. In 2013, Massironi *et al.* [5▪] published an extensive review of malnutrition in IBD. In the present review, we summarize the recent data published since then.

IRON

Anemia is the most common complication of IBD [6]. Iron deficiency is the leading cause of anemia in patients with IBD, present in 30–90% of all anemic patients with IBD. Anemia in patients with IBD is frequently multifactorial, the result of nutritional deficiencies combined with the anemia caused by the chronic disease. The relative contribution of each component is not easily established [7]. Recent studies of cohorts of patients with IBD found a high prevalence of anemia. Overall prevalence in a Romanian inpatient study found anemia to be present in 31.3% of patients [8]. Two Brazilian cohorts of outpatients found the prevalence of anemia to be 21 and 22.2% [9,10]. In these studies, 53–66% of the population with IBD had iron deficiency. Differences in prevalence found in the various studies may be attributed to differences in patient characteristics, methods, and the definitions of anemia and of the deficiencies used in these studies. In all studies, higher prevalence of iron deficiency correlated more with active disease than with remission. European Crohn's and Colitis Organization (ECCO) guidelines recommend establishing the diagnosis of iron deficiency in IBD based on ferritin levels [11]. Ferritin acts as an acute phase reactant, therefore different threshold levels are defined with regard to the level of inflammation. In patients without clinical, endoscopic, or biochemical evidence of active disease, serum ferritin less than 30 μg/l is an appropriate threshold for defining iron deficiency. In the presence of inflammation, a serum ferritin of up to 100 μg/l may still be consistent with iron deficiency, therefore other measurements, such as transferrin saturation, should be used. In recent years, new insight was gained in the understanding of anemia in chronic diseases and in its differentiation from iron-deficiency anemia. New diagnostic tools have been developed. The most prominent discoveries in the area have been hepcidin and soluble transferrin receptors (sTfR). Hepcidin is a protein identified to be acting as a central regulator of iron absorption and of its release from stores in the reticuloendothelial system. At high hepcidin levels, the duodenal absorption of iron is depressed, resulting in retention of iron in macrophages [12]. sTfR is elevated in iron-deficient states, but is significantly less affected by inflammation than typical iron indexes. Neither assay is available for routine use in most hospitals.

When iron deficiency is established, the treatment is iron supplementation. Although this seems to be a straightforward process, important questions must be answered to ensure that treatment is effective. A complaint of activity-induced fatigue is a clear indication for treatment for patients with low hemoglobin. Significantly low hemoglobin levels are considered to be below 12 g/dl in females and 13 g/dl in males [7]. In patients with non-IBD, a link was found between iron deficiency (not necessarily coupled with anemia), and fatigue, learning, and memory disturbances [13]. Specifically regarding patients with IBD, a population-based cohort study published in 2013 suggested that iron deficiency in the absence of anemia does not correlate with clinically relevant fatigue [14▪]. ECCO guidelines suggest that although there is evidence of benefit in treating iron deficiency without anemia in other conditions, such evidence is not yet available in the context of IBD, and therefore the decision to supplement iron in patients without anemia is controversial and individualized [11].

Iron supplementation can be administered orally or parenterally. For oral supplementation, the various compounds are either ferrous salts, mainly sulfate, or ferric preparations with an iron polymaltose complex. Oral supplementation is efficient in 67–78% of patients [15]. Organic iron compounds may be better tolerated than previously used traditional inorganic iron salts, making it possible to

obviate the need of parenteral treatment. Oral treatment with ferric maltol was found to be efficient and tolerable in patients with IBD with a history of failure of treatment with oral ferrous compounds. A significant improvement in hemoglobin concentration (2.25 g/dl) was observed, with adverse effects of abdominal pain, constipation, and flatulence, each occurring in less than 7% of the patients [16▪].

Several studies demonstrate the advantage of parenteral treatment over oral supplementation [17]. Different parenteral compounds are available. In previous years, parenteral iron treatment was associated with severe adverse events, including anaphylactic shock and death. At present, the most frequently used parenteral compound is ferric gluconate. Its disadvantage is the need for repeated courses of treatment, with the associated inconvenience. Iron carbohydrate compounds, for example ferric isomaltose and ferric carboxymaltose, were developed in order to diminish the number of infusions needed to treat and replenish iron stores, while retaining the efficacy and safety profile of parenteral iron. A high dose of ferric carboxymaltose was found to be well tolerated and effective in patients with IBD with iron deficiency even in a single treatment session with Infliximab infusion [15]. The efficacy of ferric isomaltose in IBD has not been proven in a direct comparison with ferric carboxymaltose. A randomized, noninferiority study of parenteral iron isomaltose compared with oral iron sulfate for treatment of anemia in patients with IBD failed to demonstrate noninferiority for achieving the primary end point of change in hemoglobin after 8 weeks [18▪▪].

ECCO guidelines recommend intravenous iron to be considered as the first line of treatment in patients with clinically active IBD, previous intolerance to oral iron, hemoglobin below 10 g/dl, or the need for erythropoiesis-stimulating agents [11]. This finding is supported by a study carried out by Iqbal *et al.* [19▪] demonstrating that patients with high baseline C-reactive protein (CRP) achieve lower hemoglobin response with oral iron therapy (increment of 3.0 vs. 4.0 g/dl, after 8 weeks of treatment) than with parenteral treatment. Reinisch *et al.* raised the question whether oral iron compounds should not serve as the first line of treatment in patients who are tolerant to oral iron and in whom a lack of response to oral iron has not been documented.

A common problem is the small percentage of patients with IBD with iron deficiency who undergo treatment. Lupu *et al.* [8] described a group of 291 adult patients suffering from IBD (40% Crohn's disease), in which anemia was present in 31% of the patients, only 30% of whom received treatment. In a German cohort of 193 patients with IBD-associated anemia (60% Crohn's disease), 43.5% of patients were treated for iron deficiency [20]. An Israeli study of 373 inpatients with IBD found that only 56% of patients with iron deficiency anemia were prescribed treatment [21].

B12 (COBALAMIN)

Battat *et al.* [22▪] summarized the cause of B12 deficiency in patients with IBD. Causes include ileal disease or resection, fistulas, small bowel bacterial overgrowth, reduced intake, increased physiologic requirements, protein-losing enteropathy, and hepatic dysfunction. Up to 22% of patients with Crohn's disease suffer from B12 deficiency when diagnosis is based on serum levels [23,24]. The percentage of patients with additional biomarkers for B12 deficiency, such as high levels of methylmalonilic acid, homocysteine, or symptoms related to B12 deficiency is much lower. A thorough systematic review, including 42 articles and a total of 3732 patients, concluded that B12 deficiency in patients with no ileal resection (or resection of <30 cm) is no more common than in the general population [22▪]. Only ileal resections greater than 20 cm predispose to B12 deficiency. The authors suggested using a diagnostic and therapeutic flow chart for making diagnosis and treatment decisions. Generally, only patients after significant ileal resection, patients with clinically suspected deficiency, and patients with elevated biomarkers should be treated with cobalamin supplements. ECCO guidelines recommend checking for cobalamin level at least annually or when macrocytosis is present, in the absence of thiopurine use [11].

FOLIC ACID

Folate deficiency is common in patients with IBD, mostly in Crohn's disease. Up to 80% of patients with Crohn's disease present with low levels of serum folate. Risk factors for deficiency include active disease and sulfasalazine or methotrexate treatment [24,25]. It has been suggested that because of folate supplementation in the flour, the prevalence of deficiency should decrease, but no study appears to document IBD levels in areas in which the flour is supplemented with folate [26]. ECCO guidelines recommend measuring folate level at least annually, or if macrocytosis is present in the absence of thiopurine use [11].

VITAMIN A

Several studies have documented a higher prevalence of vitamin A deficiency, defined by reduced

serum retinol levels, in patients with IBD than in a matched control population [27]. Levels of vitamin A are low at the time of diagnosis of IBD in children [28]. A case report of a patient with IBD with night blindness was published in 2014 [29] (the deficiency developed after several small bowel resections, and it was restored after regular parenteral vitamin A injections, also restoring normal sight). Vitamin A is stored exclusively in the liver, and serum levels are a poor indicator of body reserves. Soares-Mota *et al.* [30▪] performed a thorough investigation of vitamin A status, using the relative dose response (RDR) level as an indirect indicator of the hepatic retinol stores, together with the serum retinol level. In this functional test, the retinol level is measured before and after ingestion of a constant amount of retinyl palmitate. RDR greater than 20% was used as the cut-off point; higher levels were considered to be an indirect indication of inadequate hepatic stores. Based on this method, 37% of the patients in the Crohn's disease group had decreased retinol stores in the liver, compared with a 29% deficiency obtained by measuring blood levels alone. Patients with Crohn's disease with vitamin A deficiency showed significantly lower BMI and body fat than those with normal levels. No association was found with ileal location of disease, bowel resection, ileal resection, disease duration, and CRP level.

VITAMIN D

Vitamin D deficiency is common in the general population. Level of vitamin D is best assessed by measuring 25-hydroxy vitamin D (25-OHD). Level of less than 20 ng/ml is defined as deficiency, whereas 25-OHD = 20–30 ng/ml is defined as insufficiency. Several studies reported a high prevalence of vitamin D deficiency and insufficiency in patients with IBD, but in other studies the prevalence was not different and even lower than in the general population [31]. It has been speculated that vitamin D deficiency can lead to metabolic bone disease: osteopenia and osteoporosis. The relationship between levels of vitamin D and bone metabolic disease is not unequivocal, however. In a recent study, Tan *et al.* found lower vitamin D levels in patients with IBD. These levels correlated with disease severity but not with bone mineral density [32]. An increasing body of evidence supports the role of vitamin D in the pathogenesis of IBD. Vitamin D affects gut inflammation [33] and microbiota [34▪]. Low levels of vitamin D were associated with disease activity in several studies, including a recent cross-sectional study of 133 patients with IBD [35]. Vitamin D supplementation has the potential to reduce inflammatory response *in vivo* through its action on the cytokine profile, and could lower cytokine production [36], including serum tumor necrosis factor-α level [37]. There are preliminary reports on the clinical benefit of vitamin D supplementation in patients with Crohn's disease as an only treatment for mild disease [38] or in combination with other treatments [39].

VITAMIN K

Vitamin K deficiency has been reported in the past in patients with IBD, both ulcerative colitis and Crohn's disease. There is a correlation between active disease and propensity for vitamin K deficiency [40]. Because the main source of vitamin K is intestinal bacteria production, the cause of deficiency is probably malabsorption rather than dietary insufficiency. In Crohn's disease patients, low levels of free and bone-vitamin K are associated with low bone mineral density [41]. We found one interventional study of supplementation of phylloquinone (vitamin K1) to patients with Crohn's disease with vitamin K deficiency and low bone mass; the study found no improvement in the bone mass of the lumbar spine or the femur, although undercarboxylated osteocalcin level in the serum decreased. The interrelationship between vitamin K, bone mass, and IBD has still not been elucidated.

SELENIUM

Selenium deficiency has been described in patients with IBD. Most studies showed low mean selenium level [42], although the exact prevalence is not known. Selenium is associated with lowering gut inflammation. Experiments with selenium-deficient mice models showed exacerbation of the colitis with reduced dietary intake of selenium, and reduction in the severity of the inflammation with addition of selenium [43,44]. Other studies failed to demonstrate the benefit of selenium supplementation or showed that it increased the severity of colitis [45]. Supplementation of selenium for Crohn's disease patients has never been studied.

OTHER NUTRITIONAL DEFICIENCIES

Zinc is an essential micronutrient. Assessment of zinc status is not straightforward because its serum levels fluctuate and reflect recent intake because of the lack of storage. The search for biomarkers of zinc status lead to the identification of several candidates such as urinary zinc excretion, erythrocyte zinc concentration, platelets zinc concentration, plasma alkaline phosphatase activity, and hair zinc

concentration. The most frequent biomarker studied is zinc serum levels, other potential biomarkers were studied in a relatively small number of studies. Zinc deficiency has been described in patients with IBD, and it is estimated to occur in about 15% of patients with IBD [46]. Recently, zinc deficiency was shown to be correlated with inflammation in IBD. After a 5-year follow-up of a group of children who have been taking a standard multivitamin additive, the deficiency persisted in 37%, and 15% developed new zinc deficiency during the follow-up, while taking the multivitamin [47]. Moreover, zinc was previously found to be in relation with the inflammatory process by ameliorating the trans-mucosal leak in Crohn's disease, and by decreasing the numbers of proinflammatory cells. Most recently, it was also shown that in an in-vitro cell culture, there is an increased interleukin-1β and interleukin-6 responses following lipopolysaccharide stimulation [48].

Vitamin B1 (thiamine) deficiency was previously described in patients with IBD, mostly in those treated with parenteral nutrition [49]. Recently, a case report was published describing a patient with Crohn's disease with a clinical and radiological diagnosis of Wernicke's encephalopathy [50]. The true incidence of thiamine deficiency in patients with IBD is not known. Costantini *et al.* described a series of IBD patients with normal levels of thiamine and thiamine pyrophosphate who suffered from severe fatigue. After being treated with a high dose of oral thiamine, 10 out of 12 patients showed complete regression of fatigue, and the remaining ones showed nearly complete regression. The authors suggested other mechanisms, causing the fatigue including transport of the vitamin into the cells that are overcome by the relatively high concentration in the blood [51].

CONCLUSION

In conclusion, micronutrient deficiencies are common and have clinical significance. High suspicion of micronutrient deficiencies is recommended in order to address the treatable causes of morbidity appropriately and to prevent late and irreversible sequelae.

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Conflicts of interest

There are no conflicts of interest.

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