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Micronutrient Status and Prediction of Disease Outcome in Adults With Inflammatory Bowel Disease Receiving Biologic Therapy

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Background and Aims: Micronutrient deficiencies are common in patients with inflammatory bowel disease (IBD), but whether they relate to disease outcomes remains unknown. This study assessed the micronutrient status of adults with IBD on treatment with biologic therapies and explored predictive relationships with disease outcomes.

Methods: Seventeen micronutrients were measured in the blood of 216 adults with IBD on biologic therapy. Of these, 127 patients (58%) had Crohn's disease (CD), and the majority (70%) received treatment with infliximab. Patients were followed for 12 months and onset of adverse clinical outcomes (eg, requirement for treatment with corticosteroids, hospitalization, or surgical intervention) was recorded, and related to micronutrient status.

Results: Among all patients, the most common deficiencies were for vitamin C (n = 35 of 212 [16.5%]), ferritin (n = 27 of 189 [14.3%]), folate (n = 24 of 171 [14.0%]), and zinc (n = 27 of 210 [12.9%]). During follow-up, 22 (10%) of the 216 patients developed 1 or more adverse clinical outcomes. Patients with CD and zinc deficiency were significantly more likely to require surgery ($P = .002$) or treatment with corticosteroids ($P < .001$). In contrast, patients with ulcerative colitis and selenium deficiency were significantly more likely to have a clinical flare of disease ($P = .001$), whereas those with CD were not. This relationship with selenium remained significant after adjustment for confounders.

Conclusions: A substantial proportion of adults with IBD present deficiencies for certain micronutrients, with selenium and zinc deficiency predicting adverse disease outcomes. For other micronutrients, deficiencies were less common and should not warrant routine screening. Intervention studies should explore the effect of micronutrient supplementation in modifying disease outcomes in IBD.

Key Words: inflammatory bowel disease, micronutrients, nutrition

Introduction

The role of diet and nutritional status in inflammatory bowel disease (IBD) is an important theme, with the European Society of Clinical Nutrition and Metabolism (ESPEN) now recommending that all patients with IBD be routinely screened for micronutrient deficiencies.[1]

Nutritional deficiencies are common in patients with IBD. A Canadian study identified that hospitalized IBD patients were 6 times more likely to be protein-calorie malnourished than those hospitalized for non–IBD-related reasons.[2] This is particularly true in Crohn's disease (CD), in which inflammation frequently affects the small intestine, a site where absorption of key micronutrients takes place. Micronutrient deficiencies can also occur due to increased rate of transit time through the gut and poor oral intake due to gastrointestinal symptoms, nausea, or food aversions, particularly in patients with active disease.[3] In addition to this, food avoidance and change of dietary habits is prevalent among patients with IBD, as perceptions of disease association with diet are common.[4]

Micronutrients exert key roles in whole body homeostasis including immune and inflammatory responses, thus potentially influencing disease progression in patients at risk of deficiency. MacMaster et al[5] recently demonstrated a wide range of nutritional deficiencies in a cohort of quiescent IBD patients and showed a relationship between biochemical zinc deficiency and reduced time to a subsequent disease relapse in patients with CD.

Here, we evaluated the biochemical status of 17 micronutrients measured in the blood of adult patients on biologic therapy for IBD and explored predictive relationships with future disease outcomes.

Methods

Study Population

Following pilot introduction of the ESPEN guidelines in routine practice, the micronutrient status of adult IBD patients in the South Glasgow was audited from July to November 2020.

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Key Messages

- **What is already known?** Nutritional deficiencies are common in patients with inflammatory bowel disease (IBD), due to a range of disease- and patient-related factors.
- **What is new here?** Low selenium was associated with a more severe disease course, particularly in ulcerative colitis, and low zinc was associated with complications of Crohn's disease; whether this is as a cause or consequence of the dysbiosis associated with active IBD warrants further study.
- **How can this study help patient care?** The findings from this study add further justification for the routine testing of certain micronutrients in patients with IBD and avoiding testing for rarer, less clinically relevant micronutrients.

Eligible patients included all those attending the hospital Medical Day Unit for infusions of infliximab or vedolizumab or injections of adalimumab or ustekinumab.

Clinical data were collected from the patients' electronic patient records. Data collected included demographics, the Scottish Index of Multiple Deprivation (SIMD) score, Montreal classification of disease location and behavior, and medication information.

Plasma vitamin A, vitamin C, vitamin E-to-cholesterol ratio, total 25-OH vitamin D, vitamin K-to-triglyceride ratio, selenium, copper, and zinc; whole blood manganese and vitamin B1-to-hemoglobin (Hb) ratio; erythrocyte vitamin B2, vitamin B6, and selenium; and serum vitamin B12, magnesium, ferritin, manganese, and folate were all measured alongside routine monitoring bloods including serum albumin and C-reactive protein (CRP) as markers of disease activity. Fecal calprotectin (FCP) was noted if tested as part of routine care within 3 months of micronutrient screen.

Patients in biochemical remission at baseline were defined as those with albumin >35 g/L, CRP <10 mg/L, and FCP <250 ug/g. Those in the cohort who were deemed have stable disease were defined as having had no escalation or change in therapy for the preceding 3 months.

Clinical outcome data for the 12-month period following micronutrient screen were extracted from the electronic patient record. Deterioration of disease activity during the follow-up period was defined as a change in maintenance therapy for IBD, requirement for treatment with corticosteroids, hospitalization, or surgical intervention. As this was an appraisal of current practice with retrospective data extraction from medical notes, no contemporaneous changes were made to the patients' clinical care or micronutrient status based on the study, and the requirement for ethical approval was waived.[6]

Micronutrient Analysis

Micronutrients were assayed at the Scottish Trace Element and Micronutrient Diagnostic and Research Laboratory, a national accredited service, as has previously been described.[7] Plasma vitamin A (retinol) and E (α-tocopherol) were determined by high-performance liquid chromatography (HPLC). Plasma vitamin E was corrected for plasma total cholesterol to adjust for any variations in plasma lipids. Plasma vitamin K (phylloquinone) was assessed using liquid chromatography tandem mass spectrometry and corrected for triglyceride levels. Vitamin B1 (thiamine diphosphate) was measured in whole blood using HPLC with postcolumn ferricyanide derivatization and fluorometric detection. Vitamin B2 (flavin adenine dinucleotide) was measured in erythrocytes with isocratic HPLC with a reversed-phase C18 column and fluorescence detection. Vitamin B6 (pyridoxyl phosphate) concentrations in red cells was measured by HPLC using precolumn semicarbazide derivatization and fluorescence detection. Vitamin B2 and B6 concentrations in red cells were adjusted to Hb. Vitamin C status was measured in plasma on a C18 reversed-phase analytical column (with electrochemical detection). Vitamin D status was assessed by measuring 25-OH vitamin D by liquid chromatography tandem mass spectrometry. Inductively coupled plasma mass spectrometry (Agilent Technologies) was used to measure plasma zinc, copper, selenium, erythrocyte selenium, and whole blood manganese using germanium and scandium as an internal standard. All methods were tested and calibrated against certified reference material. The between batch coefficient of variation of all methods described previously was <10%.

Reference intervals for the measured micronutrients are shown in Table 1.

Statistical Analysis

The relationships between each micronutrient and CRP, serum albumin, FCP, and clinical outcomes were explored with Spearman's rank correlations. Chi-square test was used to explore differences in categorical data between groups. Predictions of clinical outcomes (ie, need for surgery, treatment escalation, or hospitalization) were explored using linear and logistic regression analysis. Kaplan-Meier survival analysis was used to test prediction of time to deterioration of disease activity for each micronutrient, and Cox proportional hazards regression was used to account for confounders.

Results

Participants

A total of 216 patients were included (58% male, median age 43 [interquartile range, 31-58] years). A total of 127 (58.8%) patients had CD, the majority of whom had ileocolonic disease (Montreal classification: L3). Of those with ulcerative colitis (UC), the majority had left-sided disease (Montreal classification E2) (Table 2).

Prevalence of Micronutrient Deficiencies

The most common deficiencies in the entire cohort were vitamin C (n = 35 of 212 [16.5%]), ferritin (n = 27 of 189 [14.3%]), folate (n = 24 of 171 [14.0%]), and zinc (n = 27 of 210 [12.9%]). In the cohort, 9.5% (n = 19 of 200) were deficient in vitamin B6, 7.8% (n = 13 of 166) in vitamin D with an additional 27.1% (n = 45 of 166) of patients being insufficient in vitamin D,[8] and 6.5% (n = 13 of 200) in selenium. Deficiencies of other micronutrients were uncommon (Figure 1). Among the micronutrients with the most common biochemical deficiencies, low ferritin was associated with female sex (16 of 79 females vs 11 of 110 males; $P = .047$), and folate was positively correlated with age ($r = 0.26$, $P < .01$).

High manganese was associated with UC ($P = .004$) and the vitamin E-to-cholesterol ratio was associated with CD ($P = .04$). Otherwise, micronutrient deficiencies were not related with disease location, behavior, age, or sex.

Table 1. Normal ranges of measured micronutrients according to the Scottish Trace Element and Micronutrient Diagnostic and Research Laboratory.

Micronutrient	Normal range
Folate, µg/L	3.1-20.0
Manganese, nmol/L	70-280
Zinc, µmol/L	11.0-18.0
Ferritin, µg/L	15-300
Copper, µmol/L	10.0-22.0
Magnesium, mmol/L	0.7-1.0
RBC selenium, nmol/g Hb	3.0-9.0
Plasma selenium, µmol/L	0.75-1.5
Vitamin K-to-triglyceride ratio, nmol/mmol triglyceride	0.2-2.2
Total 25-OH vitamin D, nmol/L	>25
Vitamin C, µmol/L	15-90
Vitamin E-to-cholesterol ratio, µmol/mmol cholesterol	3.5-9.5
Vitamin A, µmol/L	1.0-3.0
Vitamin B12, ng/l	200-883
RBC vitamin B6, pmol PLP/g Hb	250-680
RBC vitamin B2, nmol FAD/g Hb	1.0-3.4
Vitamin B1, ng TDP/g Hb	275-675

Abbreviations: FAD, flavin adenine dinucleotide; Hb, hemoglobin; PLP, pyridoxal 5'-phosphate; RBC, red blood cell; TDP, thiamine diphosphate.

Correlations Between Micronutrients With Markers of Disease Activity

Associations were explored between micronutrient status and frequently used markers of disease activity (CRP, serum albumin concentration, and FCP), as demonstrated in Figure 2. Significant associations were observed between CRP with the concentration of zinc, copper, and selenium in plasma; red blood cell (RBC) selenium; and vitamin K-to-triglyceride ratio, vitamin C, vitamin E-to-cholesterol ratio, vitamin A, and vitamin B1.

The concentration of serum albumin was significantly associated with plasma zinc, ferritin, selenium, and copper; RBC selenium and vitamin B2; and vitamin E-to-cholesterol ratio; and vitamin B1.

FCP was significantly associated with plasma zinc, ferritin, copper, and selenium; RBC selenium; and vitamin E-to-cholesterol ratio, vitamin A, and vitamin B1.

Micronutrient Status and Prediction of Adverse Outcomes

During the 12-month follow-up period, 22 of the 216 patients in the cohort developed 1 or more adverse clinical outcomes, consisting of a clinical flare of disease, requirement for corticosteroids, or need for surgical intervention. In logistic regression, CRP, albumin, and FCP at the point of micronutrient status assessment were all significantly associated with subsequent adverse outcomes. Vitamin A (odds ratio [OR], 0.12; 95% confidence interval [CI], 0.03-0.47; P = .002), serum copper (OR, 1.26; 95% CI, 1.12-1.40; P < .001), erythrocyte selenium (OR, 0.59; 95% CI, 0.36-0.97; P = .04), and plasma zinc (OR, 0.67; 95% CI, 0.47-0.96; P = .029) were all predictive of the need for surgery within the 12-month follow-up period. Plasma selenium (OR, 0.11; 95% CI, 0.02-0.71; P = .02), serum copper (OR, 1.19; 95% CI, 1.09-1.29; P < .001), and vitamin K-to-triglyceride ratio (OR, 0.34; 95% CI, 0.13-0.89; P = .028) were all associated with future need for treatment with corticosteroids. Subsequent clinical flare of disease was associated with selenium deficiency (OR, 0.11; 95% CI, 0.02-0.59; P = .01), vitamin A deficiency (OR, 0.55; 95% CI, 0.21-0.91; P = .03), and high serum copper (OR, 1.23; 95% CI, 1.12-1.34; P < .001).

Because the levels of several micronutrients in plasma are influenced by the systemic inflammatory response, analysis was repeated in a subset of patients (n = 48) who were in complete biochemical remission, defined as normal levels of disease biomarkers (ie, CRP, albumin and FCP). No significant associations were observed between micronutrient status and clinical outcomes in this small subset of patients.

The patient cohort was further subdivided to analyze those were felt to be clinically stable with no changes in treatment in the 3 months prior to micronutrient assessment. In the stable UC cohort (n = 57), 19.6% were deficient in vitamin C, 14.3% were folate deficient, 13.5% were ferritin deficient, and 8.9% were deficient in zinc. Eleven patients went on to have a clinical flare of disease in the 12-month follow-up period. High copper, low selenium, and low vitamin E-to-cholesterol ratio were all associated with disease flare. In multivariate analysis controlling for confounding factors (FCP, CRP, albumin, Hb, body mass index, and drug level if available) copper remained significant (P = .027). Eight patients required steroids in this cohort. Low selenium remained significantly associated with need for steroids in multivariate analysis (P = .03). No patient required surgery in the follow-up period.

A total of 110 patients with CD had stable disease. Of those, 17.8% were deficient in vitamin C, 15.5% in folate, 9.6% in vitamin D, and 6.7% in zinc. A total of 17 patients went on to have a flare of disease in the follow-up period. High CRP, low albumin, low Hb, high serum copper, and low vitamin K-to-triglyceride ratio were all significantly associated with disease flare. In multivariate analysis, only low Hb remained significant (P = .011). Seven patients from this group underwent surgery within the 12-month follow-up period. Low Hb, high CRP, high copper, and low vitamin A were associated with need for surgery. After adjustment for confounders, high copper (P = .005) and low vitamin A (P = .04) remained statistically significant. Ten patients required steroids in the follow-up period; however, there were no significant associations with micronutrient deficiencies in this group.

The findings of our logistic regression analysis were replicated using survival analysis. Patients with CD and zinc deficiency were significantly more likely to require surgery (P = .002) or induction treatment with steroids (P < .001); however, those with UC were not. Likewise, patients with UC and selenium deficiency were significantly more likely to have a clinical flare of disease (P = .001), whereas those with CD were not. (Figure 3A-D). When accounting for confounders using Cox proportional hazards regression, the significance of these findings were lost; however, this suggests that much of the effect could be driven by systemic inflammatory response.

Discussion

This study reported the prevalence of micronutrient deficiencies in the blood of a large cohort of adults with IBD on

Table 2. Participants' demographic characteristics.

	Total IBD (n = 216)	CD (n = 127)	UC (n = 77)	IBDU (n = 12)
Age, y	43 (31-58)	43 (31-60)	45.5 (34-58)	30.5 (25.5-59.5)
Sex				
Female	90 (41.7)	54 (42.5)	30 (39.0)	6 (50)
Male	126 (58.3)	73 (57.5)	47 (61.0)	6 (50)
BMI, kg/m^2	26.1 (22.9-29.4)	25.7 (22.3-28.3)	26.7 (24.0-31.5)	24.5 (23.1-29.1)
SIMD quintile				
1	50 (23.3)	28 (22.2)	18 (23.4)	4 (33.3)
2	40 (18.6)	26 (20.6)	12 (15.6)	2 (16.7)
3	23 (10.7)	14 (11.1)	8 (10.4)	1 (8.3)
4	37 (17.2)	22 (17.5)	14 (18.2)	1 (8.3)
5	65 (30.2)	36 (28.6)	25 (32.5)	4 (33.3)
CD—Montreal classification				
Age				
A1 (<16 y)	—	25 (19.7)	—	—
A2 (17-40 y)	—	72 (56.7)	—	—
A3 (>40 y)	—	30 (23.6)	—	—
Location				
L1 (ileal)	—	26 (20.5)	—	—
L2 (colonic)	—	36 (28.4)	—	—
L3 (ileocolonic)	—	65 (51.2)	—	—
Behavior				
B1 (nonstricturing/penetrating)	—	40 (31.5)	—	—
B2 (stricturing)	—	42 (33.1)	—	—
B3 (penetrating)	—	45 (35.4)	—	—
p (perianal)	—	39 (31.2)	—	—
UC—Montreal classification				
Disease extent				
E1 (proctitis)	—	—	6 (7.8)	—
E2 (left-sided colitis)	—	—	39 (50.7)	—
E3 (pancolitis)	—	—	32 (41.6)	—
Treatment				
Infliximab	152 (70.4)	105 (82.7)	40 (52.0)	7 (58.3)
Vedolizumab	61 (28.2)	19 (15.0)	37 (48.0)	5 (41.7)
Adalimumab	1 (0.5)	1 (0.8)	—	—
Ustekinumab	2 (0.9)	2 (1.6)	—	—
Azathioprine	71 (32.9)	45 (35.4)	21 (27.2)	5 (41.7)

Values are mean (interquartile range) or n (%).
Abbreviations: BMI, body mass index; CD, Crohn's disease; IBD, inflammatory bowel disease; IBDU, inflammatory bowel disease unclassified; SIMD, Scottish Index of Multiple Deprivation; UC, ulcerative colitis.

treatment with biologic therapies and subsequently explored predictive relationships with adverse disease outcomes within 12 months of follow-up. Our results show that certain micronutrient deficiencies were common in our population, but for several other micronutrients this was not the case. The most commonly seen deficiencies were vitamin C, folate, zinc, selenium, and ferritin in plasma. Of interest, the trace elements in plasma, zinc and selenium, were also related to adverse disease outcomes, including an induction course with steroid use and surgery, which indicates disease deterioration. Most importantly, these effects persisted even after correction for potential confounders, indicating their independent effects on clinical outcomes.

Previous studies have suggested that around 15% of IBD patients have subnormal serum zinc levels,[9] and therefore deficiency was possibly less frequent than may have been expected in our group. This could be due to the methods of patient selection in our study, with all patients being treated with biologic therapies and attending the medical day unit at their local hospital regularly. This could mean an increased frequency of prompt intervention from medical professionals, though we were unable to control for this in our analysis. Also, because several micronutrients in plasma are influenced by the acute phase response in ongoing systemic inflammatory conditions, the lower level of micronutrients observed in the current population, and compared with previous reports, may reflect more effective disease management in the new era of biologics.

Serum copper was seen to be high in 6.9% of patients in our cohort and high serum copper was associated with adverse outcomes, particularly in the Crohn's disease subgroup.

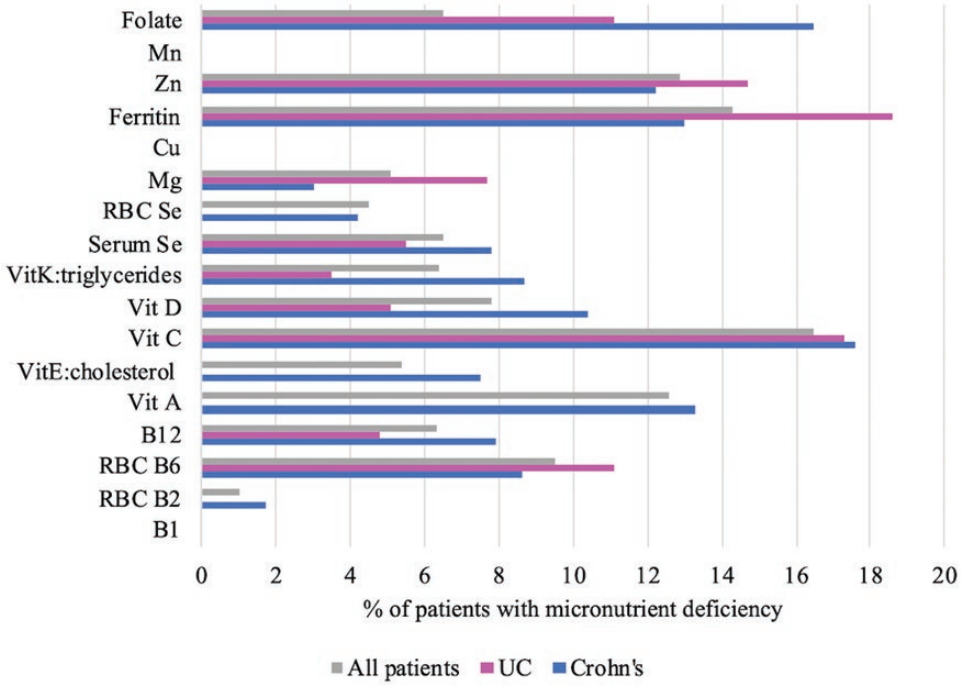

Figure 1. Prevalence of micronutrient deficiencies among all patients and divided by inflammatory bowel disease subtype. Cu, copper; Mg, magnesium; Mn, manganese; RBC, red blood cell; Se, selenium; UC, ulcerative colitis; Vit, vitamin; Zn, zinc.

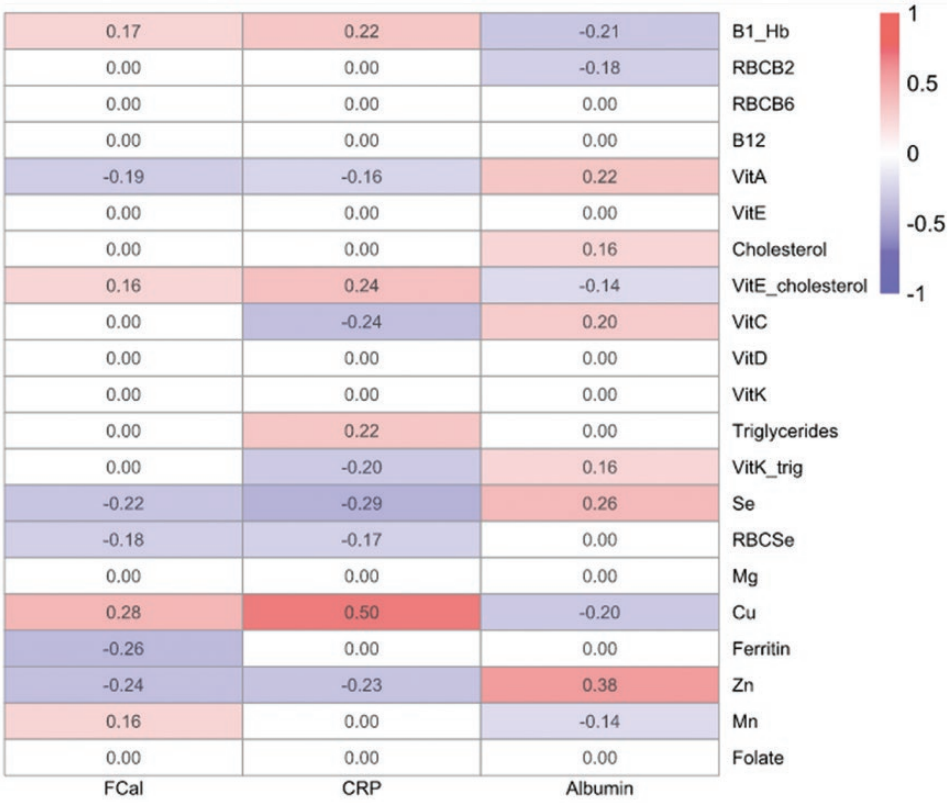

Figure 2. A heatmap of the correlations between micronutrients and markers of disease activity. Cu, copper; FCal, fecal calprotectin; Hb, hemoglobin; Mg, magnesium; Mn, manganese; RBC, red blood cell; Se, selenium; UC, ulcerative colitis; Vit, vitamin; Zn, zinc.

High serum copper levels have previously been demonstrated in pediatric IBD disease at diagnosis when compared with healthy control subjects.[10] This is most likely explained due to the role of ceruloplasmin, copper's main carrier protein in blood, as a positive acute phase reactant, meaning that levels will increase in active inflammation.[11]

Low selenium was seen as a predictor of more severe disease course in our patients with UC in particular. It is

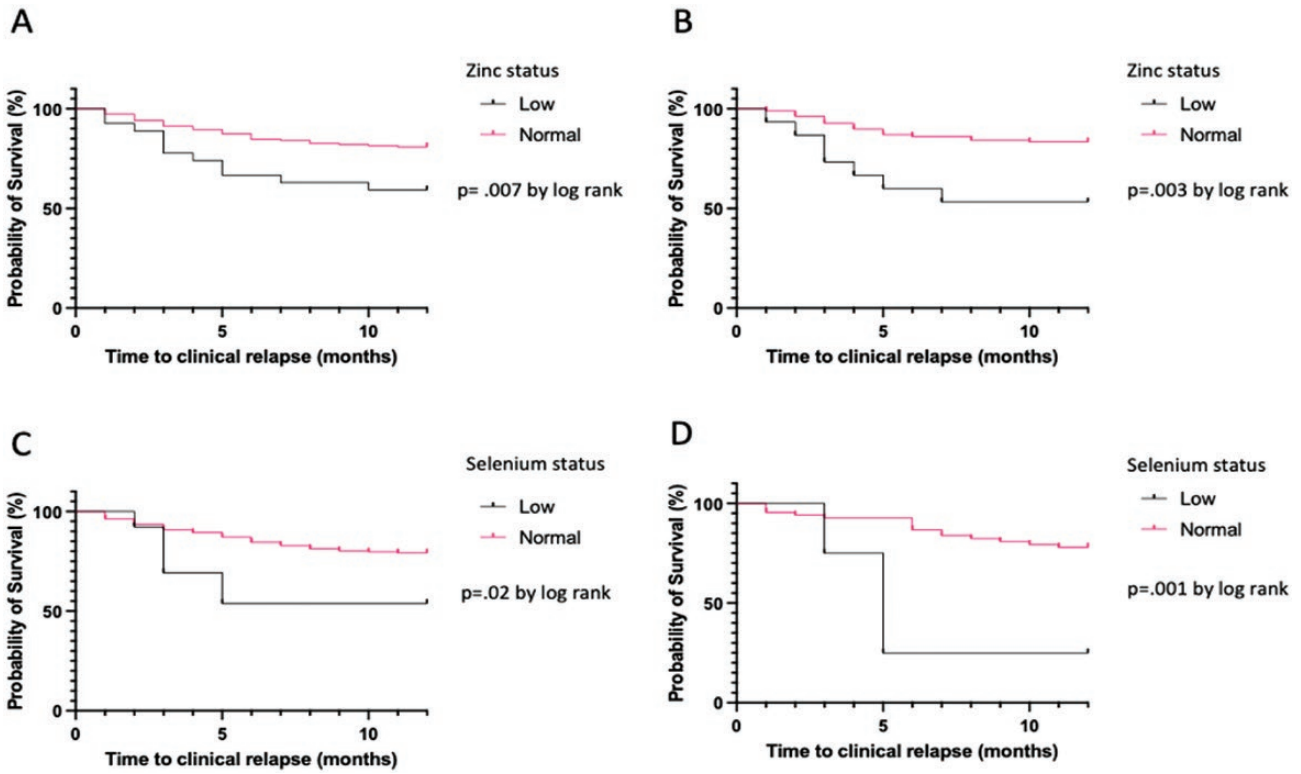

Figure 3. A, Kaplan Meier survival curve showing the time to clinical deterioration of disease among the whole cohort, stratified by zinc micronutrient status. B, Kaplan-Meier survival curve showing the time to clinical deterioration of disease, stratified by zinc micronutrient status, in only those patients with Crohn's disease. C, Kaplan-Meier survival curve showing the time to clinical deterioration of disease among the whole cohort, stratified by selenium micronutrient status. D, Kaplan-Meier survival curve showing the time to clinical deterioration of disease, stratified by selenium micronutrient status, in only those patients with ulcerative colitis.

thought that the majority of bioavailable selenium absorption takes place in the small intestine,[12] with studies in mice showing that selenium supplementation has an effect on the diversity of the gut microbiome and that conversely the microbiome composition affects the ability of the intestine to absorb selenoproteins.[13,14] Therefore, the dysbiosis seen in IBD could be associated with selenium deficiency, whether as a cause or consequence. In a large study of a Chinese cohort, *Faecalibacterium prausnizii* (a bacterium thought to have a protective effect against inflammation)[15] was seen to correlate negatively with plasma selenium levels, while plasma selenium had a negative effect on Proteobacteria, a phylum that includes several pathogens and pathobiont organisms.[16,17] It has previously been shown that while patients with both CD and UC demonstrated lower selenium levels than healthy control subjects, patients with severe and extensive UC had lower levels than those with mild localized disease, and no correlation was seen with CD severity.[18,19] Studies in mouse disease models have shown that dextran sulfate sodium– and TNBS-induced colitis were both ameliorated by a high-selenium diet.[20,21]

Zinc status has been often related with CD course. Zinc is essential to several processes in cellular metabolism, with roles in protein synthesis, wound healing, and improvement of intestinal barrier function.[22] Studies of isotopic zinc absorption from patients with CD have shown that absorption itself is impaired.[23,24] This suggests that a proportion of patients with CD may be truly deficient in addition to serum zinc levels reflecting low albumin state, and that zinc supplementation could be of increased importance in patients with IBD. In healthy volunteers, zinc supplementation stabilized gut mucosa,[25] and a prospective study of over 170 000 healthy nurses showed that there was an increased risk of developing CD with a lower daily intake of dietary zinc.[26] This could implicate zinc supplementation as a target for therapy, or even prevention of development of IBD in susceptible individuals.

Multivariate analysis also highlighted the role that systemic markers of inflammatory response have on a patient's micronutrient status. Previous reviews have demonstrated that both acute and chronic inflammatory states influence overall plasma micronutrient levels, so interpretation of blood levels can be challenging or even impossible, particularly those measured in plasma.[27] Collectively, this study reinforces the message issue that in the presence of ongoing systemic inflammatory response, interpretation of plasma measurements is difficult and may mislead clinical practice. This notion is further supported by the observation that those micronutrients measured intracellularly in erythrocytes were within normal levels for the large majority of patients. Thus, we advocate the use of the European Society of Paediatric Gastroenterology Hepatology and Nutrition decision pathway[28] to evaluate vitamin and trace element status using laboratory biomarkers prior to any clinical intervention being decided. Another important implication of the findings of the current study is that screening for deficiencies is unnecessary for a significant number of vitamins and trace elements. Because cost is a financial barrier to routine analysis of micronutrient status in IBD patients, this might add to the argument to undertake selective testing of clinically relevant micronutrients to

increase cost-effectiveness.[23] Finally, has been recognized that systemic disease biomarkers such as CRP can be less reliable surrogates of active disease, particularly CD.[29] Therefore, if certain micronutrients perform better in predicting active disease or disease progression than mainstream inflammatory markers like CRP and serum albumin, the introduction of the former in routine practice may be advantageous and inform better patients' clinical management.

Although the underlying role of these deficiencies in causing disease exacerbation needs to be addressed within a randomized controlled trial, the clinical practitioner might be able to use these micronutrient levels in addition to other disease biomarkers to predict which patients are likely to experience a disease relapse and adapt disease management strategies accordingly.

Conclusions

This study offers important insights on the recommendation made by ESPEN on analysis of micronutrient status in IBD patients on a routine basis, but only after ruling out the effect that systemic inflammatory response may have on plasma micronutrient measurements. It also generates the research hypothesis that zinc and selenium supplementation may be used to improve disease outcomes in patients with CD and UC, respectively. This may warrant further investigation as part of a randomized control trial.

Conflicts of Interest

K.G. has received research grants from, received speaker fees from, and served as a consultant for Nestlé Health Science, Nutricia-Danone, Abbott, Baxter, Servier, Janssen, and Dr Falk. None of the other authors have any sources of support to acknowledge or conflicts of interest to disclose.

Author Contribution

All authors have read and approved the final version of the manuscript.

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