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Zinc Deficiency is Associated with Poor Clinical Outcomes in Patients with Inflammatory Bowel Disease

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Abstract

Introduction—Zinc plays a pivotal role in wound repair, tissue regeneration, and the immune response. Although zinc deficiency is common in patients with inflammatory bowel disease (IBD), the impact of low serum zinc levels on disease course is not known.

Methods—Patients enrolled in a prospectively collected IBD registry with at least two serum zinc measurements were included in the analysis. Using a logistic regression model, rates of IBD-related surgeries, IBD-related hospitalizations, and IBD-related complications were evaluated following a diagnosis of zinc deficiency (serum concentration <0.66 mcg/ml) compared to those with normal zinc concentrations. In patients who were zinc deficient, outcomes were also analyzed between those who had normalization of zinc levels within 12 months and those who remained deficient.

Results—A total of 773 patients with Crohn's disease (CD) and 223 with ulcerative colitis (UC) were included in the analysis. After adjusting for covariates, zinc deficiency was associated with an increased risk of subsequent hospitalizations, surgeries, and disease-related complications in patients with CD and UC (CD: hospitalizations, OR 1.44, 95% CI [1.02-2.04]; surgeries, 2.05 [1.38-3.05]; complications, 1.50 [1.04-2.15]; UC: hospitalizations, 2.14 [1.07-4.29]; surgeries, 1.64 [0.59-4.52]; complications, 1.97 [0.94-4.11]). Normalization of zinc was associated with improvement in these outcomes in patients with both CD and UC.

Conclusion—IBD patients with serum zinc deficiency are more likely to have adverse disease-specific outcomes. As these outcomes improve with normalization of zinc, the results from this study support the role for close monitoring and replacement of zinc in patients with IBD.

Keywords

Zinc; inflammatory bowel disease; Crohn's disease; Ulcerative Colitis; Outcomes

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Introduction

Zinc is an essential trace element, which is absorbed in the small intestine and serves as a cofactor for numerous enzymes involved in growth, immune function, and tissue repair (1, 2). Zinc levels are often low in in patients with chronic diarrhea or malabsorptive disorders. Similarly, zinc deficiency is common in patients with inflammatory bowel disease (IBD) during disease and in remission, with a prevalence ranging from 15% to 40% (3-6).

Pre-clinical data as well as human studies support that zinc deficiency may contribute to mucosal inflammation in patients with IBD. In animal models, zinc deficiency exacerbates colitis and potentiates production of pro-inflammatory cytokines, including tumor necrosis factor α (TNFα) (7, 8). Furthermore, previous work indicates that a low zinc diet in healthy volunteers results in a decrease in the TH1 cytokines, IFN-γ and IL-2, as well as diminished lytic activity of natural killer cells (2). In addition to the impact of zinc on immune function, studies involving both animal models of colitis and Crohn's disease (CD) patients have demonstrated improvement in mucosal permeability with zinc supplementation (9, 10).

Despite these data supporting the role of zinc deficiency in active mucosal inflammation and epithelial barrier function, there are no studies examining clinical outcomes in patients with IBD who are zinc deficient. As such, we sought to test the hypothesis that IBD patients deficient in zinc would have poor clinical outcomes.

METHODS

Study Population

The University of Chicago Medicine Digestive Diseases Center maintains an IRB-approved prospectively collected registry of patients with IBD. We identified patients seen between 2000 and 2015 who had at least two serum zinc concentrations performed as part of their standard clinical care and at least 3 months of subsequent follow up.

Measurement of Zinc Levels

Serum zinc collected after April 2010 was measured at the Mayo Medical Laboratories (Rochester, MN) using cell dynamic reaction cell-inductively coupled plasma-mass spectrometry (DRC-ICP-MS). Prior to April 2010, zinc was measured with plasma optical emission spectrometry (ICP-OES). Zinc concentrations were defined as either normal if ≥ 0.66 mcg/ml or deficient if < 0.66 mcg/ml according to laboratory reference values.

Variables and Outcomes

Age at index zinc measurement, age at diagnosis of IBD, gender, race, smoking status, prior Crohn's-related small bowel resections, duration of disease at the time of index zinc measurement, C-reactive protein (CRP) and albumin levels measured concurrently with zinc were obtained through abstraction of the electronic medical record (EMR). Using the prescription function of the EMR, we ascertained if a patient was taking IBD-related medications including aminosalicylates, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and anti-tumor necrosis factor-α monoclonal antibodies at any time point.

Outcomes after index zinc measurement were compared between patients who were zinc deficient compared to those with normal zinc levels. In subjects who were zinc deficient on index measurement, outcomes were also assessed following a second zinc measurement and compared between subjects who corrected serum zinc levels within 12 months to those who remained deficient. Primary outcomes included IBD-related hospitalizations, IBD-related surgeries (surgical resection with or without creation of a stoma or ileoanal pouch) or IBD-related complications (including malnutrition, dehydration, anemia, hemorrhage, intestinal obstruction, fistula, abscess, and colonic stricture) using the appropriate procedure Current Procedural Terminology (CPT) codes for surgical procedures or complications. CPT codes used to identify IBD-related surgical procedures included: 45, 45.01, 45.02, 45.03, 45.61, 45.62, 45.72, 45.73, 45.74, 45.75, 45.76, 45.79, 45.80, 45.82, 45.83, 46.01, 46.03, 46.1, 46.2, 46.74, 48, 48.5, 48.52, 48.59, 48.62, 48.62, 48.69, 48.73, 48.93, 49.01, 49.11, 49.12, 49.73, 54.91, 57.83, 70.73 and 70.74. The International classification of disease (ICD)-9 codes utilized to identify IBD-related complications were 260-263, 263.1, 263.2, 263.8, 263.9, 275.2, 275.3, 276.1, 276.3, 276.52, 276.52, 276.8, 280, 280.1, 280.8, 280.9, 285.1, 285.9, 537.3, 537.4, 560, 560.1, 560.2, 560.3, 560.31, 560.32, 560.39, 560.81, 560.89, 560.9, 560.1, 567.21, 567.22, 567.23, 567.31, 567.38, 567.89, 567.9, 568, 569.2, 569.3, 569.41, 569.42, 569.49, 569.81, 569.83, 578.1 and 578.9. A chart review performed on 100 random patients in the cohort demonstrated a strong correlation between the documented CPT and ICD-9 codes and clinical description of outcomes and procedures in the electronic medical records.

Statistical Analysis

Statistical analyses were performed using Stata v14 (College Station, TX). Comparisons between groups were made using the Chi-squared test for categorical variables and Wilcoxon rank-sum test or Student’s t-test for continuous variables. For each of the three IBD-related outcomes (at least one IBD-related hospitalization, surgery, or complication), univariate logistic regression models were fit to examine associations with covariates of interest for patients with either Crohn’s disease or ulcerative colitis (UC) Covariates with $p<0.15$ in either the CD or UC univariate analysis were included in multivariate analyses in order to examine the impact of low zinc on the outcomes of interest. To account for the potential impact of differential follow-up on outcomes, duration of follow-up was included in the multivariate models. Estimated average probabilities from the multivariate models were plotted. Similar analyses were performed for those with low zinc levels comparing subjects who corrected their zinc level within 12 months to those who remained zinc deficient.

ETHICAL CONSIDERATIONS

The study was approved by the Institutional Review Board at the University of Chicago (IRB # 15-1175)

RESULTS

Study Population

773 patients with Crohn's disease and 223 patients with ulcerative colitis were included in the analysis. Median length of follow-up was 3 years for the entire cohort (IQR: 2-6 years). In subjects with CD, female sex (p=0.03), race (p=0.002), lower mean serum albumin level (p<0.001), higher median CRP concentration (p<0.001), and previous small bowel surgery (p=0.05), were associated with serum zinc deficiency. The only baseline variables associated with serum zinc deficiency in UC patients were albumin (p<0.001) and CRP levels (p<0.001). Medication usage, age, disease duration, and smoking status were not associated with zinc deficiency in either group of patients (Table 1).

Zinc deficiency is associated with an increased rate of IBD-related hospitalizations, surgeries, and complications

Overall, 31% of patients in the cohort had at least one IBD-related hospitalization, 21% had an IBD-related surgery, and 64% had an IBD-related complication in follow up after index zinc measurement. After controlling for covariates demonstrated to have an association with the outcomes of interest in a univariate analysis (Supplementary Tables 1-3), CD subjects with zinc deficiency had greater odds of having a CD-related hospitalization (p=0.04), operation (p=0.001), or complication (p=0.03) compared to those who had normal serum zinc levels. Likewise, UC patients with zinc deficiency had greater odds of having a UC-related hospitalization (p=0.03) and demonstrated a trend towards significantly increased disease-related complications (p=0.07) compared to those with normal zinc concentrations. There was not an association with subsequent operations (p=0.3) following a diagnosis of zinc deficiency in patients with UC (Table 2).

When analyzing the impact of serum zinc deficiency on location in the bowel of surgical operations, there was an association between zinc deficiency in CD and subsequent small bowel (p=0.007) as well as large bowel (p=0.03) operations. In a similar analysis in UC patients, no association was observed between low zinc levels and subsequent small bowel surgery (p=0.3), although zinc deficiency trended towards a significant association with future colon surgery (p=0.07) (supplementary Table 4).

We also investigated the influence of serum zinc deficiency on the most common IBD-related complications: malnutrition, anemia, hemorrhage, and fistula. Malnutrition and anemia were diagnosed more frequently following a diagnosis of zinc deficiency in patients with Crohn's disease. Among patients with CD, there was no association among between low zinc concentrations and future bowel hemorrhage or a diagnosis of a new and established abdominal or perianal fistula. In subjects with UC, there was not a significant association between zinc deficiency and any of the specific disease-related complications investigated (Supplementary table 5).

Normalization of serum zinc concentration is associated with improved clinical outcomes

In patients who were zinc deficient at the time of index zinc measurement, outcomes were also compared between those who corrected their zinc concentration within 12 months

compared to those who remained zinc deficient. Normalization was confirmed by at least two measurements in all patients. In patients with CD, normalization of zinc concentrations (n=76) was associated with a decrease in hospitalizations (p<0.001), surgeries (p=0.001), and disease related complications (p=0.001) compared to subjects who remained zinc deficient (n=156). Similarly, patients with UC who corrected deficient zinc concentration (n=18) had fewer hospitalizations (p=0.01) and disease-related complications (p=0.01) compared to those who remained zinc deficient (n=74). Correction of zinc deficiency, in UC patients, however, did not have a significant association with subsequent surgeries (Table 3).

DISCUSSION

In this large single-center cohort of patients with IBD, we demonstrate that serum zinc deficiency is associated with disease-related morbidity. This is reflected in an increase in hospitalizations, operations, and disease-associated complications in patients with Crohn's disease who were zinc deficient compared to those with normal zinc levels. Although patients with ulcerative colitis demonstrated a similar odds ratio for each outcome, only hospitalizations reached statistical significance, likely reflecting the smaller sample size of UC patients included in this analysis. These outcomes improved in patients with both CD and UC who were zinc deficient and had normalization of zinc levels compared to those who remained deficient.

Zinc deficiency in IBD patients may result from poor oral intake, decreased absorption, or previous small bowel resection and is thought to contribute to mucosal inflammation (3-6). Preclinical models as well as human translational studies have demonstrated that low serum zinc concentrations may exacerbate inflammation through disruption of epithelial barrier function, impaired mucosal immunity, and increasing pro-inflammatory cytokines (2) (9) (11) (12) (13, 14). Lending support to the outcomes of these mechanistic investigations, a recently published prospective study examining 17,776 healthy women who were followed over a 26-year period reported that dietary zinc supplementation was inversely associated with the risk being diagnosed with Crohn's disease (15).

As plasma and serum zinc concentrations are widely used clinically, we chose serum zinc concentrations for a comparison in this analysis given the availability of data in this patient population and its clinical relevance. Peripheral zinc concentrations are maintained by a balance of proximal gastrointestinal tract intake, fecal losses, and slow release from tissue stores (16). Although it is hypothesized that zinc within cellular metallothionein located in solid organs may be a better marker of total body stores of zinc, animal and human data have demonstrated that plasma zinc is as useful and accurate as tissue concentrations of zinc (17),(18). Furthermore, plasma zinc concentrations may reflect zinc status better during states of acute zinc depletion due to the slow equilibration of total zinc pools (16).

The results of our study further endorse the hypothesis that zinc deficiency may contribute to disease activity in patients with IBD. To our knowledge, this is the first report to examine outcomes following a diagnosis of serum zinc deficiency or after correction of serum zinc deficiency in a cohort of patients with IBD. The major strength of this study is the ability to capture outcomes in a large cohort of IBD patients followed longitudinally. Furthermore, we

were able to control for patient-specific factors known to be associated with poor outcomes in IBD, including age, sex, race, elevated CRP, use of immunomodulators or biologics, smoking status, prior resections and Montreal score in patients with Crohn's disease, and disease duration (19-28). In addition to controlling for these variables, our analyses also took into account serum albumin levels. Seventy-five to ninety-eight percent of serum zinc is bound to proteins, including albumin and alpha-2 macroglobulin (29). While alpha-2 macroglobulin is generally stable, albumin levels may fluctuate in the setting of malnutrition, surgery, or active bowel inflammation (30-33). Therefore, demonstrating that the impact of zinc on clinical outcomes occurs independent of serum albumin levels is important and not performed routinely in clinical studies focused on zinc.

Although we did control for both CRP and albumin level, which may reflect mucosal inflammation, a major limitation of this study is that we were unable to directly assess disease activity at the time of zinc measurement. As such, we cannot conclude with our study design if the poor outcomes associated with zinc deficiency occur independently of more severe mucosal inflammation at baseline. Furthermore, those with more severe disease activity may have been more likely to have a zinc level drawn, repeated, and have closer follow up which could have biased the recording of outcomes, particularly disease-associated complications. In addition, we were unable to analyze the impact of dietary intervention or zinc supplementation on peripheral zinc concentrations in this cohort of study patients. Nonetheless, we do believe that our "real world" assessment of these measures and outcomes have clinical value.

In conclusion, zinc deficiency in IBD is associated with the development of disease-related complications and subsequent normalization of zinc levels is associated with improved outcomes. These results support the practice of close monitoring of zinc concentrations in patients active IBD and adequate replacement in those who are deficient. Prospective intervention studies are needed to better understand the pathogenetic mechanisms and potential benefit of zinc replacement therapy on mucosal inflammation in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Comparison of demographics and disease specific characteristics by zinc concentration.

	Crohn's Disease			Ulcerative Colitis		
	Normal zinc (n=447)	**Low zinc (n=326)**	**P value**	**Normal zinc (n=137)**	**Low zinc (n=86)**	**P value**
Female sex	229 (51%)	192 (59%)	0.03	63 (46%)	44 (51%)	0.45
Race Caucasian African American Asian Other Unknown	375 (84%) 37 (8%) 14 (3%) 4 (1%) 17 (4%)	256 (79%) 53 (16%) 6 (2%) 6 (2%) 5 (1%)	0.002	111 (81%) 9 (7%) 9 (7%) 2 (1%) 6 (4%)	68 (79%) 6 (7%) 3 (3%) 3 (3%) 6 (7%)	0.63
IBD medications Anti-TNFα Immunomodulator	246 (55%) 179 (40%)	196 (60%) 122 (38%)	0.14 0.48	53 (39%) 59 (43%)	39 (45%) 45 (52%)	0.33 0.18
Median age at index zinc measurement, y (25%-75%)	35 (25-49)	35 (26-48)	0.90	34 (26-46)	37 (29-55)	0.13
Median duration of disease*, y (25%-75%)	10 (5-20.5)	11 (5-20)	0.40	8 (3-14)	6 (2-15)	0.38
Mean albumin ** (SD)	4.3 g/dl (0.5)	3.7g/dl (0.6)	<0.001	4.3g/dl (0.6)	3.6g/dl(0.7)	<0.001
Median CRP *** (25%-75%)	3mg/L (3-7)	7mg/L (3-24)	<0.001	3mg/L (3-7)	18.5mg/L (3-60)	<0.001
Smoking status Current Former Never	61 (14%) 83 (19%) 292 (67%)	33 (10%) 51 (16%) 241 (74%)	0.09	9 (7%) 27 (20%) 96 (73%)	6 (7%) 21 (24%) 59 (69%)	0.78
Montreal Classification **** L1 L2 L3 B1 B2 B3	67 (16.22%) 63 (15.25%) 283 (68.52%) 130 (36.01%) 103 (23.53%) 128 (35.46%)	57 (17.65%) 51 (15.79%) 215(66.56%) 93 (35.77%) 88 (33.85%) 79 (30.38%)	0.56 0.49			
Previous small bowel resection	28 (6%)	33 (10%)	0.05			

P values were calculated using the chi-squared test for categorical variables and Wilcoxon rank-sum test or Student's t-test for continuous variables. Clinical information on age of diagnosis to calculate disease duration was available in 717 subjects with CD (normal zinc, n=416; low zinc, n=301) and 189 subjects with UC (normal zinc, n=118; low zinc, n=71).

** Albumin levels were available at the time of index zinc measurement in 678 subjects with CD (normal zinc, n=390; low zinc, n=288) and 194 subjects with UC (normal zinc, n=118, low zinc, n=76).

*** CRP values were available at the time of index zinc measurement in 578 subjects with CD (normal zinc, n=333; low zinc, n=245) and 148 subjects with UC (normal zinc, n=88, low zinc, n=60).

**** Crohn's disease extent (L classification) was available in 736 subjects (normal zinc, n=413; low zinc, n=323). Disease phenotype (B classification) was available on 621 subjects with Crohn's disease (normal zinc, n=361; low zinc, n=260). SD=standard deviation.

Table 2

Association between zinc deficiency and the development of future adverse clinical outcomes.

Hospitalization		Surgery		Complication	
Crohn's Disease					
OR (95% CI)	P-value	OR (95%CI)	P-value	OR (95% CI)	P-value
1.44 (1.02,2.04)	0.04	2.03 (1.36,3.02)	0.001	1.50 (1.04,2.15)	0.03
Ulcerative Colitis					
OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
2.14 (1.07,4.29)	0.03	1.64 (0.59,4.52)	0.3	1.97 (0.94,4.11)	0.07

Using a multivariable logistic regression model, development of at least one IBD-related hospitalization, IBD-related surgery, or IBD-related complication following index zinc measurement was compared between subjects who were zinc deficient and those with normal zinc concentrations. Covariables included in the multivariate logistic regression model were those that had a $p<0.15$ in a univariate analysis. For hospitalizations, the covariates included in the logistic regression model were race, use of an anti-TNF or immunomodulator agent, categorical albumin level (missing vs. <3 vs. >3), CRP category (missing vs. <=10 vs. >10) and follow-up duration. For surgeries, the covariates analyzed were race, use of anti-TNF medications, disease duration, categorical albumin level, CRP category, follow-up duration, and prior small bowel resection for patients with Crohn's disease. Variables analyzed to assess disease complications in the logistic regression model were race, use of anti-TNF medications, smoking, categorical albumin levels, CRP category, and follow-up duration.

Table 3

Impact of normalization of serum zinc deficiency on clinical outcomes in IBD.

Hospitalization		Surgery		Complication	
Crohn's Disease (n=232)					
OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
0.15 (0.07,0.33)	< 0.001	0.06(0.02,0.18)	0.001	0.16(0.07,0.34)	0.001
Ulcerative Colitis (n=74)					
OR (95%CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
0.21(0.07,0.69)	0.01	0.41(0.13,1.31)	0.1	0.19(0.05,0.67)	0.01

Using a logistic regression model, development of at least one IBD-related hospitalization, IBD-related surgery, or IBD-related complication were compared in those that had normalization of zinc deficiency within 12 months of index zinc measurement to those that remained deficient. Odds ratios and p values for Crohn's disease patients were calculated using a multivariable model controlling for covariates. For hospitalizations, the covariates included in the model were race, use of anti-TNF or immunomodulatory agent, categorical albumin level, and follow-up duration. For surgeries, the covariates included were race, use of anti-TNF medications, duration of disease, categorical albumin level, and follow-up duration. For Crohn's-related complications, included factors in the model were race, use of anti-TNF medications, smoking, categorical albumin level, and follow-up duration. Odds ratios and p values for ulcerative colitis patients were calculated using a univariate logistic regression model given the few number of patients in the cohort who had correction of zinc deficiency (n=18).