Original Article

The association between serum zinc level and clinical features in patients with inflammatory bowel disease

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Zinc is an essential element and important for inflammatory bowel disease patients. Herein, we aimed to elucidate the correlation between serum zinc concentration and various parameters, especially the disease activity index and endoscopic scores, in these patients. We measured serum zinc concentrations in 37 patients with Crohn's disease and 64 with ulcerative colitis and retrospectively analyzed patient characteristics, blood test values, disease activity, and endoscopic scores. Hypozincemia (<80 μg/dl) was observed in 45.9% and 29.7% of patients with Crohn's disease and ulcerative colitis, respectively. Serum zinc concentration showed a weak negative correlation with Crohn's Disease Activity Index and C-reactive protein levels in Crohn's disease patients, and a weak negative correlation with white blood cell count in ulcerative colitis patients. The zinc concentrations in ulcerative colitis patients were significantly lower in Mayo endoscopic sub-score grade 2 than in grades 0 and 1. The simple endoscopic score for Crohn's disease moderately correlated with zinc concentration. In addition, serum zinc concentration showed a moderate correlation with serum albumin and Onodera's prognostic nutritional index in both Crohn's disease and ulcerative colitis patients. Serum zinc concentration clearly correlated with inflammatory bowel disease activity, endoscopy scores, and immunonutritional parameters, suggesting the importance of monitoring zinc levels.

***Key Words*:** **zinc, Crohn's disease, ulcerative colitis, hypozincemia, disease activity**

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing, immune-mediated diseases of unknown etiology. Malnutrition is common in IBD and has been associated with sarcopenia and relapse.[1–3] Diarrhea, decreased oral intake, intestinal loss of nutrients (especially protein), malabsorption, and side effects of medications are recognized causes of malnutrition in IBD patients.[1,4–6]

Zinc is an essential trace element for humans, and most of it exists in enzymes. Enzymes that require zinc for their activity are called zinc-requiring enzymes, such as deoxyribonucleic acid/ribonucleic acid (DNA/RNA) polymerase, alcohol dehydrogenase, alkaline phosphatase, carbonic anhydrase, carboxypeptidase A, matrix metallopeptidase, and superoxide dismutase. Using the proteome analysis database, it is estimated that approximately 1,000 human enzymes can be bound to zinc.[7,8] Zinc deficiency severely impairs the activities of major ectoenzymes and subsequently delays extracellular adenosine triphosphate (ATP) clearance,[9] resulting in diverse symptoms such as dermatitis, aphthous stomatitis, hair loss, loss of appetite, taste disorder, hypogonadism in males, anemia, increased susceptibility to infection, and growth disturbances in terms of weight and height in children.[10]

There have been several reports on gastrointestinal disorders and zinc,[11,12] including the usefulness of zinc preparations for quenching reactive oxygen species in gastrointestinal mucosal disorders.[13] Several studies have reported that the serum zinc concentration in IBD patients is low,[14,15] and zinc deficiency in IBD resulted in poor clinical outcomes of hospitalizations, surgeries, and disease-related complications.[16] A systematic review reported the efficacy of zinc supplement for IBD.[17] Itagaki *et al.*[18] reported that zinc enema treatment in patients with active UC accelerated mucosal healing, and Sturniolo *et al.*[19] reported that zinc supplementation in CD patients suppressed the increase in intestinal mucosal permeability.

However, reports on zinc in real-world IBD are rare, especially regarding its correlation with the disease activity index and endoscopic score. We investigated the correlation between serum zinc levels and various parameters to elucidate the actual status of low zinc levels and for efficient surveillance of low zinc levels in IBD patients.

Methods

We measured serum zinc concentration and retrospectively analyzed patient characteristics, disease activity, and other blood test values of 37 CD patients and 64 UC patients who had at least one time serum zinc concentration measurement at the Asahi University Hospital from April 2018 to March 2020. The correlation between zinc concentration and endoscopic score, simple endoscopic score for CD (SES-CD),[20] and Mayo endoscopic subscore (Mayo-ES) for UC,[21] was studied in patients who underwent endoscopy within 6 months before and after the zinc concentration measurement ($n = 16$ cases for CD, $n = 63$ cases for UC).

Hypozincemia was defined as a serum zinc concentration <80 μg/dl, <60 μg/dl was defined as zinc deficiency, and 60–79 μg/dl was defined as potential zinc deficiency according to the clinical guideline for zinc deficiency released by the Japanese Society of Clinical Nutrition in 2018.[22] For quantitative assessment of disease activity, the Crohn's Disease Activity Index

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Table 1. Patient with CD and UC clinical backgrounds

	CD† (*n* = 37)	UC§ (*n* = 64)
Gender [number (%)]		
Male	27 (73.0)	36 (56.3)
Female	10 (27.0)	28 (43.7)
Age (years)		
Mean ± SD	49.4 ± 12.8	58.2 ± 15.7
Range [number (%)]		
≤44	11 (29.7)	16 (25.0)
45–64	23 (62.2)	9 (14.1)
≥65	3 (8.1)	39 (60.9)
Onset age (years)		
Mean ± SD	31.9 ± 13.3	47.1 ± 15.7
Range [number (%)]		
≤44	29 (78.4)	28 (43.8)
45–64	8 (21.6)	27 (42.2)
≥65	0 (0.0)	9 (14.1)
Disease duration (years)		
Mean ± SD	16.9 ± 11.4	10.5 ± 9.9
Range	1–44	0–55
Body mass index		
Mean ± SD	20.5 ± 3.1	21.9 ± 14.2
Range	14.6–27.9	16.6–30.4
Disease distribution [number (%)]		
Ileal	18 (48.6)	—
Ileocolic	6 (16.2)	—
Colic	13 (35.1)	—
Total colitis	—	35 (54.7)
Left-sided	—	14 (21.9)
Proctitis	—	15 (23.4)
Disease activity [number (%)]		
Crohn's disease activity index		
<151	26 (76.5)	—
≥151	8 (23.5)	—
Lichtiger index		
<4	—	41 (66.1)
≥4	—	21 (33.9)

†Crohn's disease, §ulcerative colitis.

(CDAI)[23] was used for CD and the Lichtiger index[24,25] was used for UC. Disease activity in the CDAI and Lichtiger index were defined as values ≥151 and ≥4, respectively. We used Onodera's prognostic nutritional index (O-PNI) as an immunonutritional parameter. The formula for O-PNI is [10 × serum albumin (g/dl) + 0.005 × total lymphocyte count (/mm^3)].[26]

This study was approved by the ethics committee of the Asahi University Hospital (approval number: 20190202) and was conducted in accordance with the principles of the Helsinki Declaration of the World Medical Association and the Ethical Guidelines for Medical and Health Research Involving Human Subjects stipulated by the Ministry of Health, Labor and Welfare, JAPAN. The opt-out method was adopted for this retrospective study.

Statistical analyses were performed using an unpaired *t* test for two groups or one-way ANOVA and Tukey's multiple comparisons test for more than two groups. Statistical correlations were measured using Pearson's correlation coefficient. Its evaluation was as follows; r = |0.01–0.20| as very weak, |0.21–0.40| as weak, |0.41–0.60| as moderate, |0.61–0.80| as strong, |0.81–0.99| as very strong. Statistical significance was set at $p<0.05$. All statistical analyses were performed using the GraphPad Prism software (San Diego, CA).

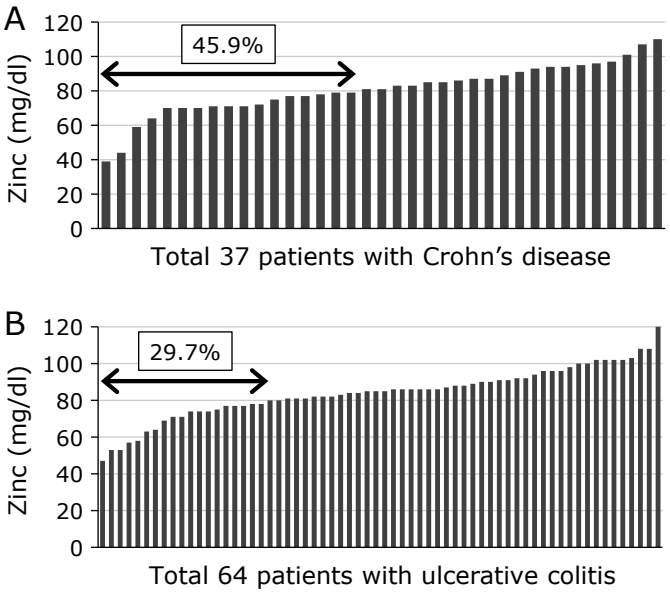

Fig. 1. Distribution of serum zinc concentration in Crohn's disease (CD) (A) and ulcerative colitis (UC) (B). Double arrow indicates the range of patients with hypozincemia (<80 μg/dl).

Results

The patients' clinical characteristics are presented in Table 1. The male-to-female ratio was roughly 3:1 for CD and 1:1 for UC. Current age and age of onset were grouped into three groups: adolescents and prime age group (44 or under), middle age group (45 to 64 years), and older age group (≥65 years). As is known, the age of onset in CD was mostly adolescent (peak in their 20s or younger; data not shown), and in UC, nearly half of the patients were less than 45 years old. On the other hand, means of current age were 49.4 years for CD patients and 58.2 years for UC patients. The percentage of patients over 45 years of age was 70.3% in the CD group and 75% in the UC group, and 60.9% of UC patients were over 65 years. The distribution of current age in our data indicates the aging of patients with IBD, which has become a global issue in recent years.[27,28]

In CD patients, zinc deficiency (<60 μg/dl) was observed in 8.1% (3 patients) and hypozincemia (<80 μg/dl) in 45.9% (17 patients) (Fig. 1A). In patients with UC, zinc deficiency was observed in 7.8% (5 patients) and hypozincemia in 29.7% (14 patients) (Fig. 1B).

We analyzed the association between serum zinc levels and patient characteristics. The correlation between body mass index (BMI) and serum zinc level in CD was weak (r = 0.32) and close to significance ($p = 0.053$). No significant correlation was found between serum zinc levels and age or disease duration in either CD or UC patients (Fig. 2A and B). There was no correlation between serum zinc level and surgical history in patients with CD. There was also no correlation between treatment with steroids, biologics, immunomodulators, or 5-aminosalicylic acid (5-ASA) in either CD or UC. However, serum zinc concentrations were significantly lower in CD patients treated with an elementary diet (Table 2).

Subsequently, we analyzed the association between serum zinc levels and disease distribution. In CD, means of serum zinc concentration in ileal, ileocolic, and colic type were 79.0, 77.0, and 85.2 μg/dl, respectively, and in UC, means of serum zinc concen-

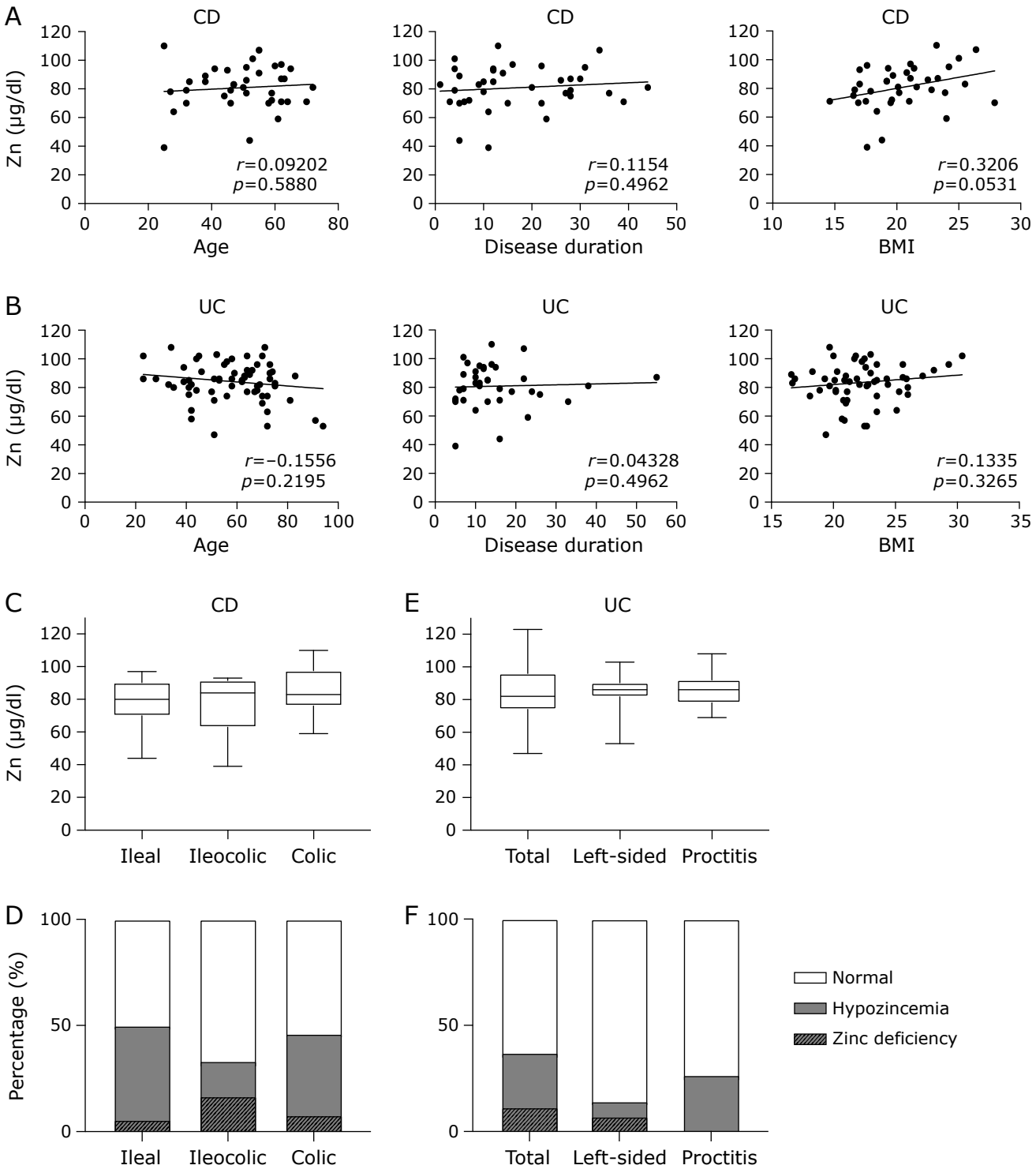

Fig. 2. Correlation between serum zinc concentration and patient age, disease duration, and body mass index (BMI) in patients with Crohn's disease (CD) (A) and ulcerative colitis (UC) (B). Comparison of serum zinc concentration and disease distribution classified as ileal, ileocolic, and colic type in CD patients (C, D) and total colitis, left-sided colitis, and proctitis type in UC patients (E, F). The lower bar graphs (D, F) show the percentage of zinc levels divided into normal (≥80 μg/dl, white color) and hypozincemia (<80 μg/dl, gray color) in which zinc deficiency (<60 μg/dl) is shown with hatched.

tration in total colitis, left-sided colitis, and proctitis type were 82.4, 85.5, and 87.1 μg/dl, respectively, which had no significant difference in both CD and UC (Fig. 2C–F).

The correlation between serum zinc concentration and inflammatory markers, C-reactive protein (CRP) level, and white blood cell (WBC) count was evaluated. Serum zinc concentration showed a weak negative correlation with CRP ($r = -0.35$, Fig. 3A), whereas there was no correlation with WBC count (Fig. 3C) in CD patients. In contrast, serum zinc concentration showed a significant negative correlation with WBC count ($r = -0.35$,

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Table 2. Serum zinc concentration and clinical characteristics in CD and UC patients

	CD† (*n* = 37)			UC§ (*n* = 64)		
	n	Mean ± SD (μg/dl)	*p* value	n	Mean ± SD (μg/dl)	*p* value
Operation history						
No	21	83.6 ± 13.5	0.401	64		
Yes	16	77.2 ± 16.5		—		
Treatment with elemental diet						
No	20	85.8 ± 13.5	0.027*	64		
Yes	17	75.0 ± 14.8		—		
Treatment with 5-ASA‡						
No	8	88.9 ± 11.8	0.069	1	69.0 ± 0.00	0.281
Yes	29	78.3 ± 14.0		63	84.5 ± 14.0	
Treatment with immunomodulator						
No	27	90.0 ± 14.0	0.377	46	83.9 ± 13.5	0.811
Yes	10	78.3 ± 16.2		18	84.9 ± 15.4	
Treatment with biologics						
No	7	79.3 ± 8.80	0.766	56	84.7 ± 14.2	0.483
Yes	30	81.2 ± 16.2		8	80.9 ± 12.9	
Treatment with steroid						
No	29	80.8 ± 16.2	0.952	48	85.3 ± 13.9	0.274
Yes	8	81.1 ± 7.70		16	80.8 ± 14.3	

†Crohn's disease, §ulcerative colitis, ‡5-aminosalicylic acid, *$p<0.05$.

Fig. 3G), with a clear increase in hypozincemia (75%, Fig. 3H), and no correlation with CRP (Fig. 3E) in UC patients. The correlation between serum zinc concentration and disease activity was evaluated. Serum zinc concentration showed a weak negative correlation with CDAI in CD patients ($r = -0.35$, Fig. 4A), whereas there was no correlation with the Lichtiger index in UC patients (Fig. 4C). In the active CDAI group, hypozincemia was present in 75% of the cases (Fig. 4B). Comparison of serum zinc concentrations between inactive and active groups revealed that the means of zinc levels were above 80 mg/dl in inactive group and blow 80 mg/dl in active group in both CD and UC patients, but no significant differences were found (data not shown). The correlation between serum zinc concentration and endoscopic scores was investigated. There was a moderate negative correlation between SES-CD and zinc concentration ($r = -0.60$, Fig. 4E). Zinc concentration in UC patients was significantly lower in Mayo-ES grade 2 than in grades 0 and 1 ($p<0.0001$ and $p = 0.0001$, respectively, Fig. 4F).

Finally, we analyzed the correlation between serum zinc concentration and nutritional status. Serum zinc concentration showed a moderate correlation with serum albumin levels in both CD ($r = 0.63$) and UC ($r = 0.62$) patients (Fig. 5A and B). The O-PNI is widely used for the assessment of immune-nutritional conditions, which can be easily calculated using the serum albumin level and peripheral blood total lymphocyte counts. The O-PNI was originally used to evaluate the risk of postoperative complications and mortality in gastrointestinal tract surgery of malnourished cancer patients[26]; however, several recent studies have reported that the O-PNI is useful for risk evaluation of postoperative complications and length of hospital stay in CD patients.[29,30] Serum zinc concentration showed a moderate correlation with the O-PNI in both CD ($r = 0.61$) and UC ($r = 0.43$) patients (Fig. 5C and D).

Discussion

In this study, hypozincemia was found in 46% of patients with CD and in 30% of UC patients with UC. Serum zinc levels were correlated with CDAI in patients with CD and WBC count in patients with UC. Serum zinc levels showed a significant association with the endoscopic scores and also correlated with immunonutritional parameters in both CD and UC patients. This is the first study to report a correlation between serum zinc levels and O-PNI or endoscopic scores in IBD patients. These results suggest that more attention should be paid to hypozincemia in IBD patients and that hypozincemia can be predicted by routine clinical measures, such as complete blood count, serum albumin, disease activity by interview, and endoscopic score.

In this study, 45.9% of patients with CD and 29.7% of patients with UC were having hypozincemia (<80 μg/dl). A study from the US reported that 42.2% of CD and 38.6% of UC patients were zinc deficient,[16] and another study reported zinc deficiency in 40% of IBD patients.[14] Although our data were from the Japanese population, the results are similar. For reference, the zinc concentration in healthy subjects is given below. The overall mean (mean ± SE, mg/dl) of serum zinc concentrations in healthy subjects reported from the United States (US) was 82.7 ± 0.6, and by gender and age: 87.2 ± 1.6 in 14–18 years (y), 87.0 ± 1.4 in 19–30 y, 85.9 ± 1.3 in 31–50 y, 83.7 ± 1.5 in 51–70 y, and 81.8 ± 1.8 in 71 y and older for males, and 81.2 ± 1.3 in 14–18 y, 79.0 ± 1.1 in 19–30 y, 80.0 ± 0.8 in 31–50 y, 81.2 ± 1.3 in 51–70 y, and 81.5 ± 1.2 in 71 y and older for females.[31]

Age has been reported to be associated with serum zinc concentration. In the US, serum zinc levels decrease slowly during adulthood and dropped after 65–70 years of age (data were analyzed from more than 10,000 people).[32] A Japanese study revealed that serum zinc levels fell remarkably with age after 60 years (data were analyzed from more than 1,000 people).[33] As summarized in Table 1, the aging of IBD patients has become a global issue in recent years.[27,28] Thus, we expected that serum zinc concentrations would decrease with aging in IBD patients as well as in the general population. However, in this study, a decrease in serum zinc concentrations was not observed in CD patients, and the very weak inclination of a decrease in serum zinc concentrations in UC patients was not statistically significant. The reason for this conclusion is the much smaller sample size in this study compared to the above-mentioned studies, and the low proportion of elderly patients in the CD group (only

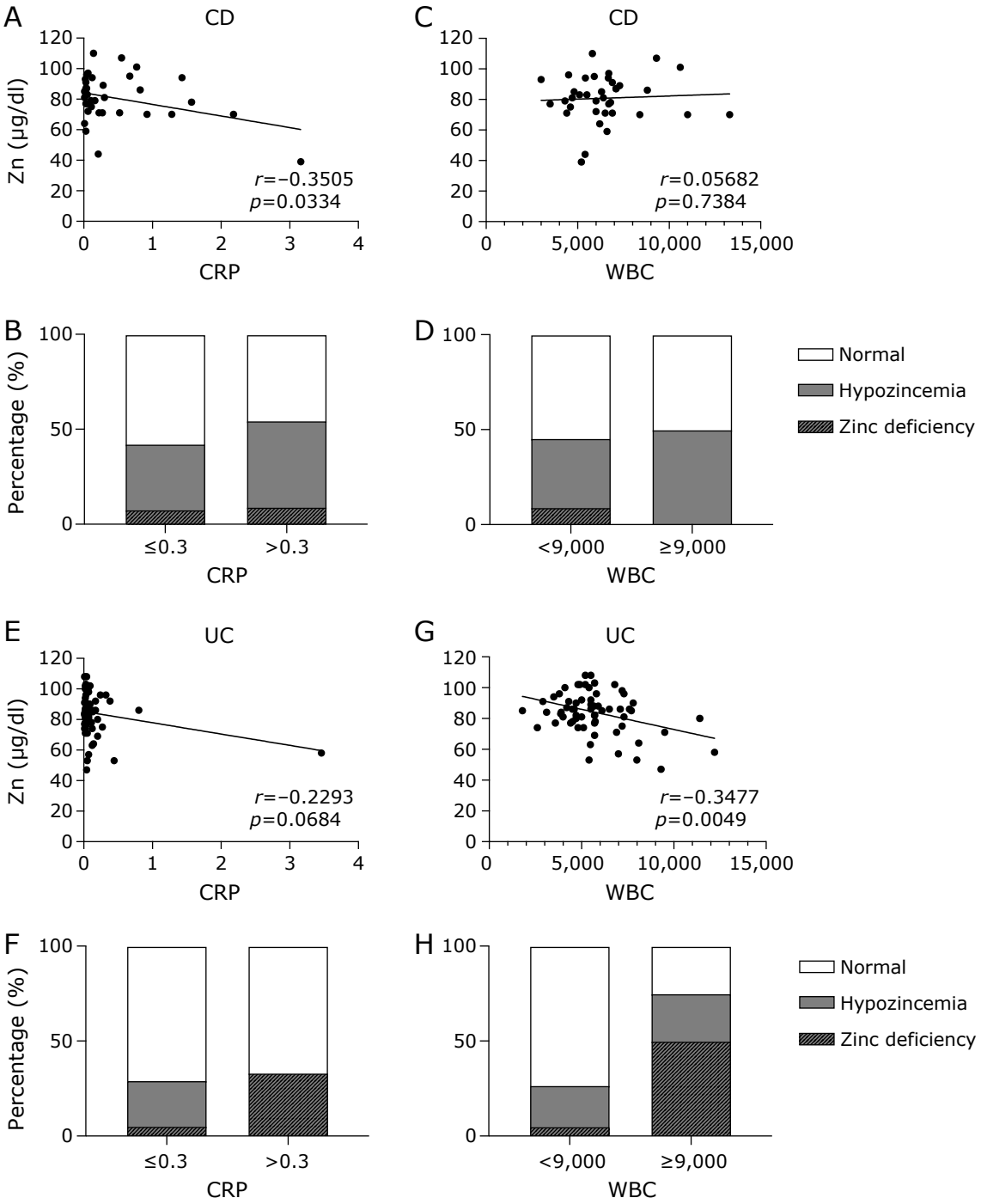

Fig. 3. Correlation between serum zinc concentration and C-reactive protein (CRP) level and white blood cell (WBC) count in patients with Crohn's disease (CD; A and C, respectively) and ulcerative colitis (UC; E and G, respectively). Each of the lower bar graphs (B, D, F, H) show the percentage of zinc levels divided into normal (≥80 μg/dl, white color) and hypozincemia (<80 μg/dl, gray color), in which zinc deficiency (<60 μg/dl) is shown with hatched, while normal and high CRP levels or WBC count correspond to the respective upper scatter plots. Abnormal high CRP level and WBC count was defined as values >0.3 and ≥9,000, respectively.

two patients were above 65 years of age). We should further pay more attention to serum zinc concentrations in patients with IBD, particularly the elderly.

Disease duration was not significantly correlated with zinc levels in either CD or UC patients. The patients using of IBD medications, such as steroids and biologics, as well as those having a surgical history, did not develop hypozincemia. Appropriate disease control using medications or surgery after onset may be the key to maintaining proper zinc concentration.

We have shown a weak correlation between BMI and zinc level in CD patients. Patients with poor oral intake would naturally have poor zinc intake as well. On the other hand, in this study, zinc level was also significantly lower in the patients treated with an elementary diet. This suggests that oral intake is not the only issue, but that the efficiency of zinc absorption in the intestinal tract must also be taken into consideration. The small

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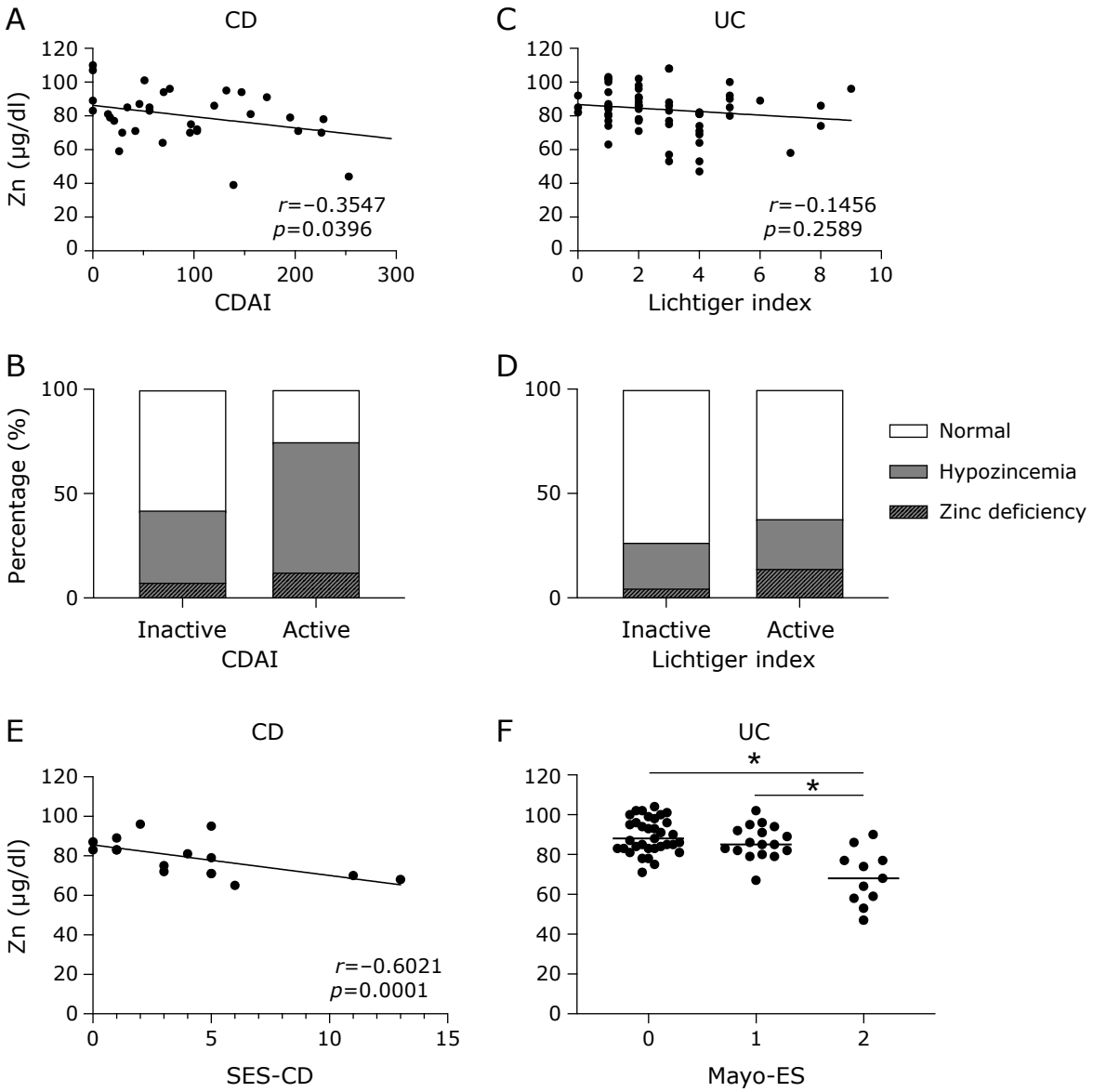

Fig. 4. Correlation of serum zinc concentration with disease activity and endoscopic score in patients with Crohn's disease (CD) and ulcerative colitis (UC). For disease activity, Crohn's Disease Activity Index (CDAI) and Lichtiger index were used for CD (A, B) and UC (C, D), respectively. The lower bar graphs (B, D) show the percentage of zinc levels divided into normal (≥80 μg/dl, white color) and hypozincemia (<80 μg/dl, gray color), in which zinc deficiency (<60 μg/dl) is shown with hatched, for active and inactive. Disease activity according to the CDAI and Lichtiger index was defined as values ≥151 and ≥4, respectively. For endoscopic score, simple endoscopic score for Crohn's disease (SES-CD) and Mayo endoscopic subscore (Mayo-ES) were used in CD patients (E) and UC patients (F), respectively. *p<0.05 (Tukey's test).

intestine is the main place for the absorption and excretion of zinc,[34,35] thus, IBD induced intestinal damage would affect zinc absorption. Usually, an elemental diet is prescribed for CD patients in whom the digestive and absorptive status of the intestinal tract is considered poor. The elemental diet used in this study was ELENTAL® (EA Pharma Co., Ltd., Tokyo, Japan), with a zinc content of 1.8 mg per package, and the average amount of ELENTAL® used in this study was 2.5 packages (range: 1–5 packages, data not shown). In general, the recommended intake of zinc in Japan is 8–11 mg/day, and the recommended dosage in treatment guidelines for hypozincemia is 50–100 mg/day orally.[22] In essence, the usual amount of elemental diet is insufficient for zinc supplementation in hypozincemia cases where intestinal malabsorption is anticipated, such as in CD, and proactive measurement of serum zinc concentration and tailored zinc administration are desirable in such cases.

Regarding disease activity, CDAI and CRP in CD patients and WBC count in UC patients were negatively correlated with serum zinc concentration. In this study, many UC patients were in remission (CRP >0.4 was in only three cases), which may be one of the reasons for the non-significant correlation between the activity index or CRP and serum zinc concentration. Chronic zinc deficiency increases the levels of pro-inflammatory cytokines via NF-κB, which is targeted by zinc.[36] Gammoh and Rink[37] reported that zinc prevents the dissociation of NF-κB from its corresponding inhibitory protein; thus, preventing the nuclear translocation of NF-κB and inhibiting subsequent inflammation.

This study is the first to examine the association between zinc levels and endoscopic scores in patients with IBD. Serum zinc levels correlated with endoscopic scores in both CD and UC patients in this study. We suggest that zinc levels should be measured in CD when SES-CD is greater than 7 and in UC when

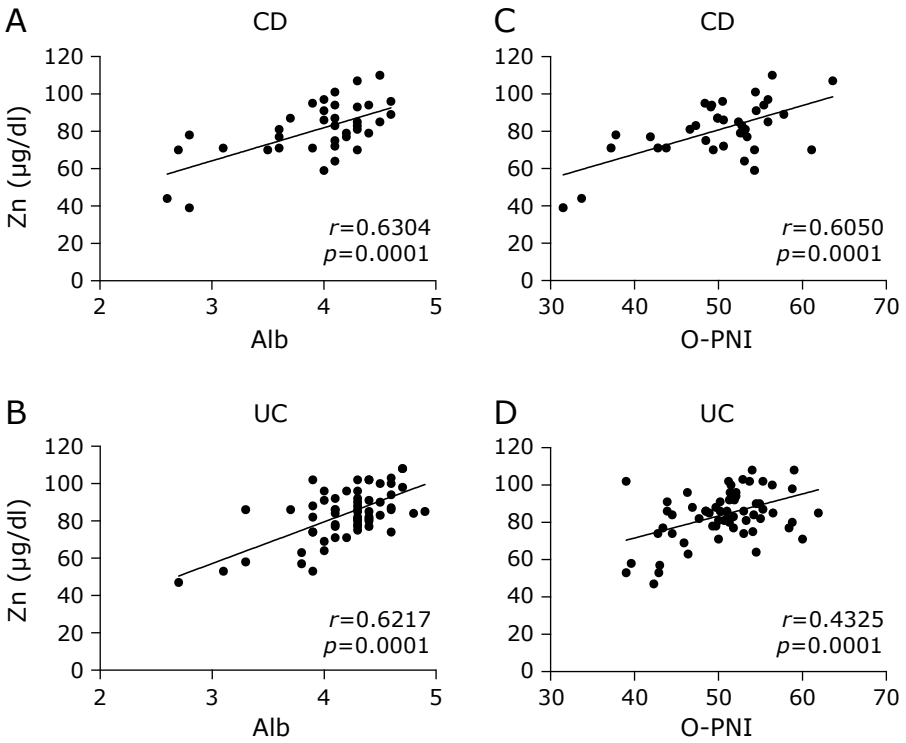

Fig. 5. Correlation between serum zinc concentration and serum albumin (Alb) and Onodera's prognostic nutritional index (O-PNI) in patients with Crohn's disease (CD, A and C, respectively) and ulcerative colitis (UC, B and D, respectively).

Mayo-ES is greater than 2.

A correlation between serum zinc and albumin, a simple nutritional indicator, has been reported.[38,39] Since 60–70% of serum zinc is bound to albumin,[40] it is not surprising that low serum albumin was associated with a risk of low serum zinc in this study. Because inadequate protein intake can cause low albumin levels, zinc deficiency may require not only supplementation of zinc but also appropriate protein intake and absorption. In this study, we included the O-PNI as an immunonutritional index. Although there have been reports of the use of the O-PNI to predict operative risk and length of hospital stay in patients with CD,[29,30] this study is the first to examine its correlation with serum zinc levels. In this study, the O-PNI, which was calculated using albumin and lymphocyte counts, also correlated well with serum zinc levels. Zinc deficiency is characterized by damage to the T cell lineage.[36,41] Among these T cell lineages, Th17 cells have been reported to be involved in the pathogenesis of IBD.[42,43] Higashimura *et al.*[44] reported that zinc deficiency activates the IL-23/Th17 axis by activating interferon regulatory factor 5.

Zinc homeostasis is not only affected by zinc intake but also by protein metabolism and inflammation. In IBD, low zinc levels due to malnutrition caused by inadequate disease control form a vicious cycle that leads to exacerbated inflammation and imbalance of the T cell lineage. During the treatment of IBD, serum albumin and/or O-PNI, which are routine parameters, should be monitored constantly, and zinc levels should be checked immediately if they are low. To maintain serum zinc levels in IBD, it is important to suppress disease activity with appropriate treatment, including the administration of biologics, and to improve nutritional status. A meta-analysis study on the prevalence of zinc deficiency in IBD reviled that one of two patients suffers from zinc deficiency,[45] and zinc deficiency in IBD resulted in poor clinical outcomes of hospitalizations, surgeries, and disease-related complications.[16] Brownson *et al.*[46] reported that 12.9% of IBD patients on biologic therapy had zinc deficiency, and patients with CD and zinc deficiency were significantly more likely to require surgery or treatment with corticosteroids. There are several reports of zinc administration to IBD patients. Sturniolo *et al.*[19] reported that oral administration of zinc improved intestinal permeability in patients with CD, as specified by the lactulose/mannitol ratio as an indicator. Itagaki *et al.*[18] reported that zinc enema treatment in patients with active UC significantly improved Mayo scores and modified Matts' endoscopic scores, indicating that zinc treatment accelerates mucosal healing. Sakurai *et al.*[47] reported that zinc administration significantly improved CDAI scores in patients with CD as well as increased serum zinc levels. Thus, since zinc administration contributes to the improvement of the pathophysiology of IBD, it is very important to determine the zinc levels of IBD patients in daily clinical practice. On the other hand, problems due to excessive zinc intake have also been reported. Excessive zinc intake can cause copper deficiency, which can result in neurological symptoms and anemia.[48] More than half of the IBD patients in this study had normal zinc levels, thus zinc should only be administered to patients with low serum zinc levels.

Limitations of this study include the single-center, retrospective nature of the study and the small number of patients, especially those with CD. For more precise data, a large-scale, multicenter study should be performed. In a future study, we aim to examine the changes in each parameter by normalizing serum zinc levels.

In conclusion, we reported the actual status of low zinc levels in patients with IBD and clarified its correlation with immunonutritional parameters and endoscopic scores. When low serum albumin or mucosal inflammation is observed in daily clinical practice of IBD, it is desirable to check the zinc level, and zinc supplementation should be considered to ameliorate pathological control.

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Abbreviations

5-ASA	5-aminosalicylic acid
ATP	adenosine triphosphate
BMI	body mass index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRP	C-reactive protein
DNA	deoxyribonucleic acid
IBD	inflammatory bowel disease
Mayo-ES	Mayo endoscopic subscore
O-PNI	Onodera's prognostic nutritional index
RNA	ribonucleic acid
SES-CD	simple endoscopic score for CD
UC	ulcerative colitis
WBC	white blood cell

Conflict of Interest

No potential conflicts of interest were disclosed.

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