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Efficacy of zinc acetate hydrate for hypozincemia in the elderly is influenced by the initial accumulated exposure dose after taking zinc acetate hydrate

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This study aimed to determine the efficacy of zinc acetate hydrate (ZAH) for hypozincemia in elderly hospitalized patients with an accumulated exposure of < 1000 mg of ZAH and to explore the factors affecting the therapeutic efficacy of ZAH. Seventy-four patients (mean age, 82 years) were enrolled in this study. All patients (n = 74) had low serum zinc levels (< 80 µg/dL), and the mean serum zinc concentration before ZAH administration was 53.6±10.7 µg/dL. The median serum zinc level (µg/dL) elevated per tablet (25 mg) of ZAH was 1.26 µg/dL, and the patients were divided into two groups, the slightly increased (< 1.26) and significantly increased (≥ 1.26) groups, based on the median cutoff value for the median increase in serum zinc level. A significant difference was found between the slightly increased (0.63±0.35 µg/dL, n = 36) and significantly increased (2.37±0.95 µg/dL, n = 38) groups (p < 0.0001, Wilcoxon rank-sum test). Logistic regression analysis with the accumulated exposure dose of ZAH, sex, and body weight as multivariate variables showed a significant difference in the accumulated exposure dose (total number of tablets per 25 mg: odds ratio, 1.119; 95% confidence interval, 1.052–1.203; p = 0.0009). There was no effect of underlying disease or of diet or zinc-containing intravenous or enteral nutrition on serum zinc levels. These results suggest that at an accumulated exposure of < 1000 mg of ZAH, serum zinc levels tend to increase with smaller accumulated doses. Therefore, serum zinc concentrations should be measured at the accumulated exposure to 500–1000 mg after ZAH initiation for the treatment of zinc deficiency in elderly hospitalized patients.

1. Introduction

Zinc is an essential trace element in the body involved in the regulation of physiological responses, such as the immune response (Overbeck et al. 2008). Zinc deficiency is associated with diseases like taste disorders and loss of appetite (Kinomoto et al. 2010; Levenson 2003). Approximately 25% of the world's population is at risk of zinc deficiency (Maret and Sandstead 2006; Wuehler et al. 2005). In recent years, the number of patients with zinc deficiency has increased in developing and developed countries (Tuerk and Fazel 2009). In an US study of 14,770 individuals aged 3–74 years, the prevalence of zinc deficiency was approximately 1–3% (Pilch and Senti 1985). In the United States, 10% of the population has serum zinc levels less than half the recommended level and is therefore at risk for zinc deficiency (Wakimoto and Block 2001). Zinc acetate hydrate (ZAH) is effective against infections and wound healing associated with hypozincemia (Nowak et al. 2012; Song et al. 2020). Zinc is required for the activity of ornithine transcarbamylase, which is involved in ammonia metabolism by the urea cycle in the liver. ZAH reduces blood ammonia levels in patients with cirrhosis (Katayama et al. 2014). Results of a meta-analysis of randomized controlled trials have demonstrated that in patients with diabetes, zinc supplementation modestly lowers glucose levels and decreases hemoglobin A1c levels (Capdor et al. 2013). The efficacy of ZAH on renal anemia has also been reported (Sato et al. 2022).

According to a previous study, the total dose of ZAH influenced the efficacy of ZAH in elderly hospitalized patients (So et al. 2022). Elevated serum zinc levels per 25 mg ZAH were higher when the accumulated exposure dose of ZAH was < 1000 mg. This included 36% of the patients with low elevation.

Therefore, focusing on patients with an accumulated exposure dose of < 1000 mg after starting ZAH for hypozincemia, we aimed to investigate the factors influencing the improvement of serum zinc levels for a new population designed in the present study. Furthermore, a retrospective analysis was performed to determine the effects of disease (Al-Marouf and Al-Sharbatti 2006; Damianaki et al. 2020; Katayama 2004; Naber et al. 1998) and nutritional status affecting serum zinc levels on the efficacy of ZAH.

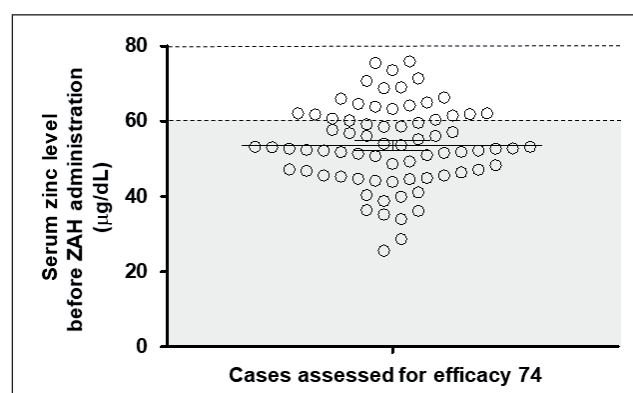


Fig. 1: Serum zinc levels before ZAH administration in elderly inpatients (n = 74). The dotted lines and gray area in the figure indicate subclinical zinc deficiency (60–80 µg/dL) and zinc deficiency (<60 µg/dL), respectively. The horizontal line with the bars represents the mean ± standard deviation of the patients.

Table 1: Baseline characteristics of the patients in this study and a previous study^{a)}

Characteristic	Present study (n =74)	Previous study (n =79) ^{a)}
Number of male patients	30 (41%)	38 (48%)
Age	82 ± 9 (54-96)	82 ± 9 (50-98)
Body weight (kg)	47.0 ± 11.2	50.9 ± 13.5
Serum albumin (g/dL)	2.8 ± 0.6	2.8 ± 0.6
e-GFR (mL/min)	78.6 ± 49.4	59.4 ± 47.1
CKD stage G4&G5 (e-GFR < 30 mL/min)	12 (16.2%)	26 (32.9%)
Average of daily zinc dose (mg/d)	52.0 ± 15.0	52.6 ± 18.0
Administration period (d)	9.6 ± 4.8 (2-24)	16.6 ± 10.6 (5-51)
Number of days from the date of the pre-administration test to the date of administration (d)	1.6 ± 2.4 (0-13)	6.3 ± 6.0 (1-32)
Number of zinc deficiency (<60 µg/dL)	52 (70%)	53 (67%)
Number of marginal zinc deficiency (60-80 µg/dL)	22 (30%)	26 (33%)
Serum levels of zinc before supplement zinc acetate (µL/dL)	53.6 ± 10.7	53.4 ± 11.5
Underlying diseases affecting serum zinc levels		
Renal disease	27 (36.5%)	ND
Diabetes	19 (25.7%)	ND
Chronic liver disease	2 (2.7%)	ND

Each value represents the mean ± standard deviation, the number of patients with the percentage or ranges in parentheses. CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate. ND: not determined. ^{a)}The value was taken from our previous report (So et al. 2022).

2. Investigation and results

2.1. Patient background

Of the 252 hospitalized patients who received ZAH, 178 met the exclusion criteria, including 99 patients with an accumulated dose of < 1000 mg and whose serum zinc level was not measured after ZAH initiation, 68 who did not start receiving the drug for the first time after hospital admission, 10 who were taking concomitant medications that interacted with ZAH and were taking ferrous sodium citrate, and 1 who discontinued ZAH owing to adverse drug reactions, such as skin rash. Ultimately, 74 patients were included in this study.

To compare the efficacy of ZAH and its affecting factors, the patient backgrounds of this study and a previous study (So et al. 2022) are shown in Table 1. Compared to the previous study, the renal function of the patient was preserved and the duration of ZAH administration

and time to serum zinc level measurement were shorter. As shown in Fig. 1, all patients (n = 74) had low serum zinc levels (< 80 µg/dL), and the mean serum zinc level before ZAH administration was 53.6±10.7 µg/dL. Hypozincemia was the most common cause (n = 31, 41.9%), followed by decreased appetite (n = 18, 24.3%). Other common symptoms included infection (n = 15, 20.2%), anemia (n = 6, 8.1%), and pressure ulcers (n = 4, 5.4%).

Table 2 shows the drugs used in combination with ZAH in this study and in a previous study (So et al. 2022). More than half of all patients used acid secretion inhibitors. Among them, proton pump inhibitors were used most frequently. Diuretics were concomitantly used in 19 (25.7%) patients, with furosemide being used most frequently. Compared with the previous study (So et al. 2022), a larger proportion of acid secretion inhibitors and smaller proportion of diuretics were used in the present study.

Table 2: Drugs combined with ZAH in this study and a previous study^{a)}

Drug	Present study		Previous study ^{a)}	
	Percentage	Number of patients (n =74)	Percentage	Number of patients (n =79)
Use of gastric acid secretion suppression drugs	63.5%	47	53.2%	42
Kinds of gastric acid secretion inhibitor drugs		27		26
Proton pump inhibitors				
Potassium-competitive acid blockers		14		12
Histamine H2-receptor antagonists		6		4
Use of diuretics	25.7%	19	39.2%	31
Kinds of diuretics				
Azosemide		5		16
Carperitide		-		2
Eplerenone		-		1
Furosemide		11		15
Spironolactone		5		9
Thiazide		1		2
Tolvaptan		9		7
Torsemide		2		2

^{a)}The value was taken from our previous report (So et al. 2022).

Table 3: Drugs for intravenous or enteral nutrition containing zinc

Route	Number of patients (n=21)	Product Name	Zinc content (mg)	Volume (mL)	Company
Drip infusion	11	BFLUID®	0.16	500	Otsuka Pharmaceutical Factory
	1	ELNEOPA®	1.95	1000	Otsuka Pharmaceutical Factory
Enteral nutrition	6	ENSURE LIQUID®	3.75	250	Abbott Japan
Drip infusion + Enteral nutrition	2	BFLUID® +ENSURE LIQUID®	0.16+3.75	500+250	Otsuka Pharmaceutical Factory Abbott Japan
	1	BFLUID® +ENORAS®	0.16+3.90	500+187.5	Otsuka Pharmaceutical Factory

2.2. Improvement in serum zinc levels with zinc acetate hydrate (ZAH) doses of < 1000 mg

The serum zinc levels increased in all patients after ZAH administration. The median serum zinc level increase per tablet (25 mg) of ZAH calculated from Eq. (2) was 1.26 µg/dL, and the patients were divided into the slightly increased (< 1.26) and significantly increased (≥ 1.26) groups based on the median cutoff value for the median increase in serum zinc level. A significant difference was found between the slightly increased (0.63±0.35 µg/dL, n = 36) and significantly increased (2.37±0.95 µg/dL, n = 38) groups (p < 0.0001, Wilcoxon rank-sum test) (Fig. 2).

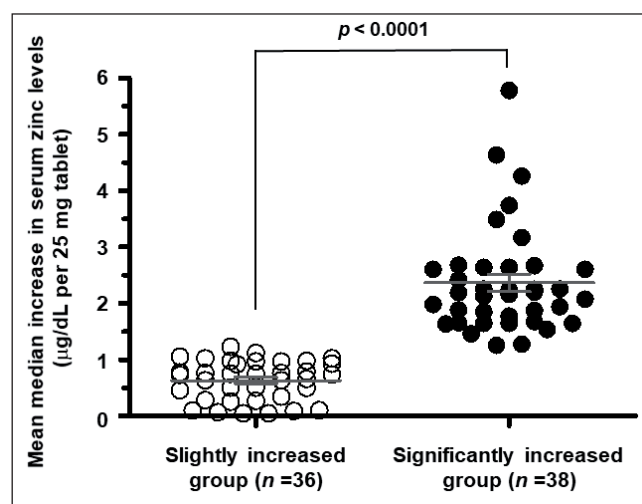


Fig. 2: Elevated serum zinc levels standardized per ZAH tablet (25 mg). The horizontal line with the bars was represents the mean ± standard deviation of the patients.

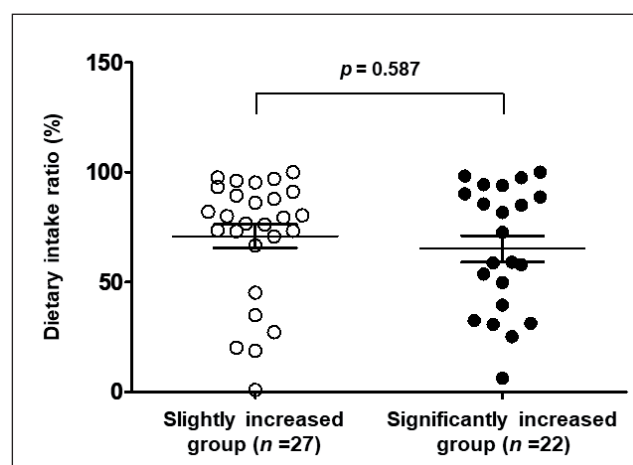


Fig. 3: Effect of dietary intake ratio on the elevated serum zinc groups. The horizontal line with the bars was represents the mean ± standard deviation of the patients.

2.3. Nutritional status

Of the 74 patients, 70 received oral intake, 3 were food deprived, and 1 received enteral nutrition. As shown in Table 3, 21 of the 70 patients who received oral intake were receiving zinc-containing drip infusion or enteral nutrition. Three patients simultaneously received both drip infusion and enteral nutrition.

The percentage of food intake in 49 of the 70 patients with only oral intake (70 patients) was compared between the slightly and significantly increased groups (Fig. 3). No significant differences were found between the slightly (70.9±27.5%) and significantly increased (65.1±28.4%) groups (p = 0.587, Wilcoxon rank-sum test).

Table 4: Factors that cause a significant increase in serum zinc levels after receiving ZAH for hypozincemia in the multivariate logistic regression analysis

Variable	Univariate analysis			Multivariate analysis		
	Crude OR	95% CI	p value (* p < 0.1)	Adjusted OR	95% CI	p value (** p < 0.05)
Male (vs. Female)	2.743	1.051 - 7.157	0.039 *	2.473	0.732 - 8.361	0.1451
Age per years	0.967	0.913 - 1.021	0.237			
Body weight per kg	1.062	1.013 - 1.123	0.022 *	1.052	0.998 - 1.120	0.0803
Accumulated expose dose (total numbers of tablets per 1 tablet=25 mg)	1.096	1.038 - 1.166	0.002 *	1.119	1.052 - 1.203	0.0009 **
Serum albumin per g/dL	1.302	0.623 - 2.778	0.485			
Serum level of zinc before supplement zinc acetate per µg/dL	1.032	0.988 - 1.081	0.165			
CKD stage (Stage G4&5 vs. Stage G1-3)	1.067	0.310 - 3.673	0.919			
Use of acid secretion inhibiting drug (vs. none)	1.304	0.504 - 3.374	0.584			
Use of diuretics (vs. none)	1.650	0.575 - 4.734	0.352			
Underlying diseases affecting serum zinc levels (vs. none)	2.161	0.853 - 5.473	0.104			
Zinc-containing combined intravenous and enteral nutrition (vs. none)	0.549	0.196 - 1.543	0.256			

OR: odds ratio, CI: confidence interval, CKD: chronic kidney disease.

2.4. Factors influencing improvement of serum zinc levels with ZAH doses of < 1000 mg

Univariate logistic regression analysis showed no significant differences between the two groups, with the dependent variable being the slightly and significantly increased groups and the explanatory variables being the presence or absence of zinc-containing drip infusion and enteral nutrition (odds ratio, 0.549; 95% confidence interval [CI], 0.196–1.543; $p = 0.256$) (Table 4). Table 4 presents the factors with a risk rate of $p < 0.1$ in each univariate logistic regression analysis, including the accumulated dose, sex, and weight. Multivariate logistic regression analysis of these factors showed significant differences in the accumulated dosage (total number of tablets per 25 mg; odds ratio, 1.119; 95% CI, 1.052–1.203; $p = 0.0009$).

Serum zinc levels tended to be less elevated as the accumulated dosage of ZAH increased (Fig. 4).

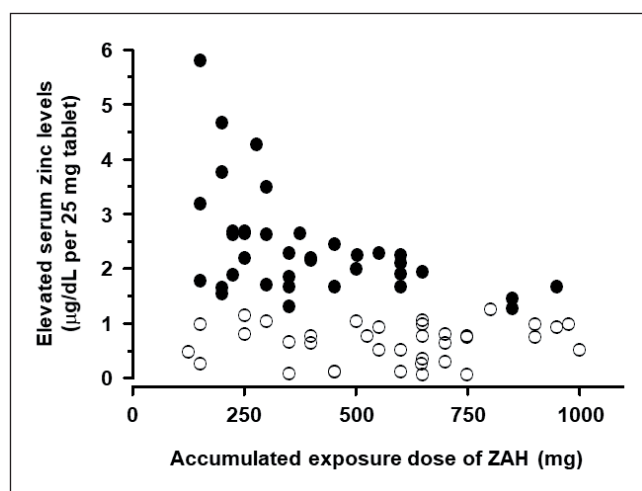


Fig. 4: Relationship between an accumulated exposure dose of ZAH and standardized elevated serum zinc concentration. The opened and closed circles represent the groups showing slight and significant increases, respectively.

3. Discussion

We previously reported that the accumulated dosage was a factor affecting the efficacy of ZAH for hypozincemia in elderly hospitalized patients (So et al. 2022). We found that the elevated value of serum zinc concentration per 25 mg of ZAH was higher when the accumulated dosage of ZAH was < 1000 mg. In the present study, a new retrospective analysis was performed to explore the factors affecting the efficacy of ZAH and its replacement therapy, focusing on the accumulated ZAH dosage of < 1000 mg. The serum zinc level ($\mu\text{g}/\text{dL}$) increase per tablet (25 mg) of ZAH was approximately four times higher in the significantly increased group ($2.37 \mu\text{g}/\text{dL}$) compared with the slightly increased group ($0.63 \mu\text{g}/\text{dL}$) (Fig. 3). An important finding was that after the initiation of ZAH, even if the accumulate dose was < 1000 mg, the factor affecting its efficacy was the accumulated dose (total number of tablets per 25 mg; odds ratio, 1.119) (Table 4). Furthermore, the present study demonstrates that diseases affecting serum zinc levels and nutritional status are unlikely to influence the efficacy of ZAH.

The present results support the following report on zinc absorption. Unlike iron and copper, zinc does not require a redox reaction for absorption from the gastrointestinal tract and is transported into cells by the Zrt-, Irt-like protein 4 (ZIP4) transporter expressed on the intestinal epithelial cell membrane (Cousins 2010). Zinc homeostasis is regulated by this transporter. Zinc deficiency promotes translation of ZIP4 mRNA and accumulation of the ZIP4 transporter in the apical membrane of intestinal epithelial cells. Endocytosis of this transporter is inhibited when zinc is deficient, but it is rapidly degraded by endocytosis when zinc is sufficient (Weaver et al. 2007). Hambidge et al. demonstrated this mechanism

in humans using “saturation response modeling” (Hambidge et al. 2010). Liuzzi et al. demonstrated this mechanism in rats by regulating the zinc transporter and other proteins involved in zinc transport in the small intestine (Liuzzi et al. 2004; Liuzzi and Cousins 2004). For these reasons, it is possible that the accumulated exposure dose of ZAH is not reflected in the increase in serum zinc concentrations because zinc may be saturated in tissues, blood, and other body fluids in the slightly increased group.

A unique feature of this study is that the efficacy of ZAH at an accumulate dose of < 1000 mg for hypozincemia in the elderly was highly reproducible (Fig. 4) when a similar analysis was performed in another population with similar patient background to the previous one (So et al. 2022). Based on the univariate logistic regression analysis, diseases, dietary intake status, and zinc-containing intravenous or enteral nutrition that affect serum zinc levels had little effect on the efficacy of ZAH (Table 4).

In the univariate analysis, body weight was significantly different (odds ratio, 1.062; 95% CI, 1.013–1.123; $p = 0.022$) as a factor affecting the increase in serum zinc levels with ZAH, indicating that serum zinc levels are less likely to increase with increasing body weight (Table 4). In contrast, no significant differences were found in the multivariate analysis. The patient weight in this study was the total body weight, including fat mass, suggesting that multivariate analysis shows no significant differences. Exchangeable zinc pools (EZPs) as a mathematical approximation of the mass of zinc compartments in the body that rapidly exchange with serum zinc are positively correlated with lean body mass (Pinna et al. 2001).

Sex was significantly different in the univariate analysis (male vs. female: odds ratio, 2.743; 95% CI, 1.051–7.157; $p = 0.039$) as a factor affecting the increase in serum zinc levels with ZAH, with males being less likely to have increased serum zinc levels than females. In contrast, no significant differences were found in the multivariate analysis. EZIP in adults is associated with multiple factors, such as body weight, age, sex, and serum zinc levels. In terms of sex, EZIP is greater in males than females, and the association decreases with age (Miller et al. 2017). EZIP is positively correlated with lean body mass (Pinna et al. 2001), and in the elderly, men tend to gain more weight, excluding fat, than women (Tanimoto et al. 2010). The effect of sex difference on serum zinc levels was observed only in young adults and was significantly lower in females than in males (Kurasawa et al. 2005). This study included elderly subjects (82 ± 9 years), and significant differences were found between the body weights of males (53.4 ± 12.3 kg) and females (42.7 ± 8.0 kg) ($p < 0.0001$, Student’s t-test). Therefore, the sex factor did not influence the increase in serum zinc levels with ZAH, and the multivariate analysis suggested that the confounding effect of lean body mass was significant.

In this study, among the patients ($n = 52$) with zinc deficiency ($< 60 \mu\text{g}/\text{dL}$), approximately 40% ($n = 21$) of these patients taking ZAH (data not shown) improved their serum zinc concentrations to normal, a result similar to that reported previously (So et al. 2022). The mean accumulated dose and duration of treatment required for this improvement were 510 ± 237 mg and 9 days (median), respectively. Although we proposed in our report (So et al. 2022) the need to evaluate serum zinc levels to confirm improvement of zinc deficiency at the accumulated dose of 1000 mg after initiation of dosing, the present results show that patients improved even earlier. That is, if 50 mg per day is administered as the starting dose of ZAH, the accumulated dose becomes 500 mg after 10 days of administration. Therefore, serum zinc levels should be measured once the accumulated dose reaches 500–1000 mg (10–20 days after ZAH initiation). Figure 5 presents the slight distribution of an initial dose of < 500 mg in the slightly increased group (Fisher’s exact test, $p = 0.0021$).

In this study, the effect of ZAH was not affected by diet or zinc-containing intravenous or enteral nutrition, indicating that ZAH is highly effective in treating hypozincemia (Fig. 3). The efficiency of zinc absorption by taking zinc supplements dissolved

as an aqueous solution is significantly higher than that of zinc from the diet, as up to 20 mg is efficiently absorbed, but at higher doses, it is less easily absorbed (Tran et al. 2004). A limitation of this study is that the quantitative effects of intravenous and enteral nutrition could not be completely ruled out in individual cases, and the continued use of ZAH should be investigated in cases of zinc deficiency that have improved with ZAH administration.

In conclusion, the accumulated dose of ZAH is an influential factor in the increase in serum zinc levels in elderly patients after the initiation of ZAH treatment with the accumulated dose of < 1000 mg. Moreover, diseases and nutritional status affecting serum zinc levels have little influence on the efficacy of ZAH. Furthermore, improvement of zinc deficiency is observed in some patients at the accumulated doses of < 500 mg. Therefore, this study suggests the need to confirm improvement in zinc deficiency at the accumulated dose of 500–1000 mg after the initiation of ZAH to ensure appropriate use of ZAH and reduce drug costs.

4. Experimental

4.1. Ethical considerations

This multi-institutional retrospective study was approved by the Research Ethics Committee, Faculty of Medicine, Juntendo University (approval no.: E22-0232-G01) and Nihon University (School of Pharmacy, approval no.: 22A-006). The analysis data of this study were strictly managed to prevent leakage to outside parties and were used only for the purpose of this study in compliance with the “Guidelines for the Appropriate Handling of Personal Information by Medical and Nursing Care Professionals.”

4.2. Subjects and exclusion criteria

This study comprised inpatients who were started on ZAH (Novelzine® tablets, 25 mg, Nobelpharma K.K., Tokyo, Japan) for the treatment of hypozincemia between April 2020 and March 2022 at Juntendo Tokyo Koto Geriatric Medical Center, Tokyo, Japan. The exclusion criteria were as follows:

- 1) Patients whose serum zinc levels were not evaluated before and after the administration of ZAH at an accumulated dose of < 1000 mg.
- 2) Patients whose serum zinc levels were not evaluated before and after treatment with polaprezinc, tetracyclines, fluoroquinolones, cefdinir, iron formulations, bisphosphonates, eltrombopag olamine, and dolutegravir sodium.
- 3) Patients who did not start receiving the drug for the first time after hospital admission.
- 4) Patients who discontinued due to side effects.

4.3. Patient background

Patients' sex, age, body weight, daily dose of ZAH, history of usage of acid-suppressing drugs and diuretics, main diseases that led to ZAH administration, and time of serum zinc level measurement before and after ZAH administration were investigated (So et al. 2022). In this study, diabetes mellitus, renal disease, chronic liver disease, and chronic inflammatory bowel disease were investigated as diseases affecting serum zinc levels. Nutritional intake during ZAH administration was also investigated. Patients' dietary intake was defined as 10 points for each whole main and side meal (total 20 points), and the number of meals per day was defined as three (maximum 60 points/day). Dietary intake was determined by nurses' records. The percentage of dietary intake during the ZAH administration period was calculated from Equation 1:

$$\text{Percentage of dietary intake (\%)} = \frac{\text{total dietary intake during ZAH administration}}{\text{number of days of ZAH administered} \times 60 \text{ points}} \times 100 \quad \text{Eq. (1)}$$

4.4. Clinical findings

Serum zinc concentration was measured using the colorimetric method, and serum albumin and creatinine levels and eGFR were investigated, as reported previously (So et al. 2022).

4.5. Evaluation of improvement of serum zinc level by ZAH administration

The serum zinc level increase per tablet (25 mg) of ZAH was calculated using Equation 2, as reported previously (So et al. 2022):

$$\text{Serum zinc level increased per ZAH tablet (25 mg)} = \frac{\text{serum zinc level after ZAH administration} - \text{serum zinc level before ZAH administration}}{\text{accumulated dose [mg] during ZAH administration period/tablet [25 mg] of ZAH}} \quad \text{Eq. (2)}$$

4.6. Statistical analyses

Univariate logistic regression analysis was first performed to identify the factors influencing the improvement in serum zinc levels during the initial period of ZAH administration. The median cutoff value for the median increase in serum zinc level per tablet (25 mg) of ZAH was used as the dependent variable for the slightly and

significantly increased groups. The independent variables were sex, age, body weight, accumulated dose per 25 mg (1 tablet) of ZAH, serum albumin level, serum zinc level before administration, renal impairment group (defined as chronic kidney disease CKD stages G4 and 5) (Levey et al. 2005), presence or absence of concomitant medications. The following variables were used in this study: concomitant medications (acid secretion inhibitors, diuretics), concomitant diseases affecting serum zinc levels, and concomitant zinc-containing intravenous or enteral nutrition. The daily dose of ZAH was evaluated as the accumulated dose per 25 mg (1 tablet) of ZAH, since the daily dose of ZAH was different for each patient. Therefore, the duration of administration was excluded from this analysis. Multivariate logistic regression analysis was subsequently performed using the factors that indicated $p < 0.1$ from the results of the univariate logistics regression analysis. JMP Pro version 16.0.0 (SAS Institute Inc., NC, USA) was used for the statistical analyses, and the significance level in the final logistic regression analysis was set at a risk rate of $p < 0.05$.

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Conflicts of interest: None reported.

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ORIGINAL ARTICLES

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