Research Square

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Effect of zinc histidine hydrate in maintenance hemodialysis patients with hypozincemia

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Abstract

Background

Zinc is an essential trace element involved in numerous physiological processes, including immune function, wound healing, and protein synthesis. Hypozincemia is common in patients undergoing maintenance hemodialysis; however, evidence regarding the clinical effects of zinc supplementation in this population remains limited. This study aimed to investigate the prevalence of hypozincemia and evaluate the effects of zinc histidine hydrate.

Methods

We retrospectively analyzed clinical data from 269 patients undergoing maintenance hemodialysis at three facilities. Associations between serum zinc concentrations and other laboratory parameters were assessed. In addition, changes in laboratory parameters were evaluated in 53 patients who received zinc histidine hydrate for 3 months.

Results

The mean serum zinc concentration was 70 ± 18 μg/dL. Serum zinc concentrations were below 80 μg/dL in 81.8% of patients. After 3 months of treatment, serum zinc concentrations increased significantly from 58 ± 9 to 96 ± 37 μg/dL ($P < 0.001$). Serum alkaline phosphatase concentrations also increased significantly, from 79 ± 37 to 87 ± 44 U/L ($P = 0.004$). Serum copper concentrations decreased significantly from 95 ± 18 to 86 ± 22 μg/dL ($P < 0.001$). One of the 54 patients who initiated treatment discontinued it because of nausea.

Conclusions

Hypozincemia was prevalent among patients undergoing maintenance hemodialysis. Zinc histidine hydrate treatment was associated with increased serum zinc and alkaline phosphatase concentrations and decreased serum copper concentrations. Monitoring serum copper during treatment is important.

Background

Zinc is an essential trace element that serves as a cofactor for more than 300 enzymes and plays important roles in protein synthesis, cell growth, and metabolism. It is also involved in immune function, wound healing, and the maintenance of normal taste perception [1, 2]. Zinc deficiency is associated with various clinical manifestations, including taste disturbances, anorexia, dermatitis, alopecia, impaired immune function, and anemia, which may adversely affect quality of life. Chronic zinc deficiency may also contribute to poor nutritional status and deterioration in overall health [1–4].

It has been reported that approximately 51.0% of Japanese hemodialysis patients have serum zinc levels below 60 μg/dL, indicating zinc deficiency [5]. These findings suggest that hypozincemia is highly prevalent in this population. Serum zinc concentrations of 60 to less than 80 μg/dL are classified as indicating latent zinc deficiency [6]. Based on this definition, more than 90% of patients undergoing dialysis have been reported to have hypozincemia [5, 7]. Possible causes include reduced dietary zinc intake due to dietary restrictions and impaired absorption related to concomitant medications [8].

In general, the risk of inadequate zinc intake is low in healthy individuals with a normal diet; however, a substantial proportion of hemodialysis patients are reported to have zinc deficiency. Nevertheless, data on the frequency of zinc deficiency–related symptoms and the clinical efficacy of zinc supplementation remain limited [3, 9, 10]. Zinc histidine was approved in August 2024 and is administered once daily, with a relatively low incidence of adverse effects such as gastrointestinal symptoms, making it an easy-to-use agent [6]. However, there have been no reports demonstrating its efficacy in hemodialysis patients to date.

Therefore, we assessed the prevalence of hypozincemia and investigated factors associated with serum zinc concentrations in patients undergoing maintenance hemodialysis. We also evaluated changes in serum zinc concentrations and other laboratory parameters following treatment with zinc histidine hydrate in patients who consented to treatment.

Methods

We reviewed the medical records of 269 patients at Towa Dialysis Clinic, Tohto Kasukabe Hospital and Tohto Sangenjaya Clinic between November 2024 and January 2025 to investigate their serum zinc and other biochemical and hematological parameters. Serum zinc concentrations were classified as follows: zinc deficiency, less than 60 μg/dL; latent zinc deficiency, 60 to less than 80 μg/dL; and 80 μg/dL or higher. To evaluate the associations between serum zinc levels and other factors, Pearson's correlation coefficients were calculated to assess the associations between serum zinc concentrations and the other laboratory parameters. Additionally, among 54 patients who initiated zinc histidine hydrate treatment, 53 completed the 3-month treatment period and were included in the before-and-after analysis. One patient discontinued treatment because of nausea and was excluded from this analysis. Zinc histidine hydrate administration was recommended to patients at the discretion of their attending physician, and was administered only to patients who consented to oral administration.

Continuous variables are expressed as means ± standard deviations. Pearson's correlation coefficient was used to assess linear associations between serum zinc concentrations and other continuous variables. Changes in laboratory parameters before and after treatment with zinc histidine hydrate were evaluated using the Wilcoxon signed-rank test. All statistical analyses were performed using JMP 5.1 software. A p-value of less than 0.05 was considered statistically significant. This study was conducted in accordance with the Declaration of Helsinki and was approved by the research ethics committee of Sangenjaya hospital (Approval No. R0801).

Results

Patient characteristics and prevalence of hypozincemia

Patient characteristics are shown in Table 1. The mean age of the participants was 70.1 ± 12.3 years, and the most common primary kidney disease was diabetic nephropathy (42.8%).

Table 1. Patient characteristics

Characteristic	Value
Male/Female, n	189 / 80
Age (years)	70.1 ± 12.3
Duration of hemodialysis (years)	7.9 ± 8.4
Primary cause of ESKD, n (%)	
Chronic glomerulonephritis	55 (20.4)
Diabetic nephropathy	115 (42.8)
Nephrosclerosis	50 (18.6)
Polycystic kidney disease	18 (6.7)
Rapidly progressive glomerulonephritis	4 (1.5)
Unknown or others	27 (10.0)

Values are expressed as mean ± standard deviation or number (%), as appropriate.

ESKD: end-stage kidney disease

Laboratory findings are summarized in Table 2. The mean serum zinc and copper concentrations were 70 ± 18 μg/dL and 95 ± 22 μg/dL, respectively. Among the 269 patients, 63 (23.4%) had serum zinc concentrations below 60 μg/dL, while 157 (58.4%) had concentrations of 60 to less than 80 μg/dL. Overall, 220 patients (81.8%) had serum zinc concentrations below 80 μg/dL.

Table 2. Laboratory characteristics of the study population

Characteristic	Quantity
Albumin (g/dL)	3.5 ± 0.4
Urea nitrogen (mg/dL)	63.6 ± 17
Creatinine (mg/dL)	9.67 ± 2.68
Alkaline phosphatase (U/L)	79 ± 40
LDL cholesterol (mg/dL)	77 ± 28
HDL cholesterol (mg/dL)	48 ± 19
Triglycerides (mg/dL)	122 ± 81
C-Reactive Protein (mg/dL)	0.48 ± 0.94
Hemoglobin (g/dL)	10.7 ± 1.3
Zinc (µg/dL)	70 ± 18
Copper (µg/dL)	95 ± 22

Values are expressed as mean ± standard deviation.

LDL: low-density lipoprotein

HDL: high-density lipoprotein

Factors associated with serum zinc concentrations

Univariate analyses of factors associated with serum zinc levels are presented in Table 3. Serum zinc levels were negatively correlated with serum copper levels ($r = -0.269$, 95% CI, −0.376 to −0.154; $P < 0.001$) and C-reactive protein (CRP) levels ($r = -0.126$, 95% CI, −0.242 to −0.006; $P = 0.039$). In contrast, serum zinc levels were positively correlated with serum albumin levels ($r = 0.147$, 95% CI, 0.027 to 0.262; $P = 0.016$). No statistically significant correlations were observed between serum zinc levels and the other variables examined.

Table 3. Univariate correlations between serum zinc levels and other variables

Variable	Correlation coefficient (r)	95% CI	P value
Albumin (g/dL)	0.147	0.027 to 0.262	0.016
Urea nitrogen (mg/dL)	-0.046	-0.183 to 0.092	0.518
Creatinine (mg/dL)	0.068	-0.052 to 0.186	0.266
Alkaline phosphatase (U/L)	-0.088	-0.206 to 0.032	0.151
LDL cholesterol (mg/dL)	0.01	-0.110 to 0.129	0.872
HDL cholesterol (mg/dL)	-0.003	-0.123 to 0.116	0.957
Triglycerides (mg/dL)	0.093	-0.027 to 0.210	0.128
C-reactive protein (mg/dL)	-0.126	-0.242 to -0.006	0.039
Hemoglobin (g/dL)	-0.078	-0.196 to 0.042	0.203
Copper (μg/dL)	-0.269	-0.376 to -0.154	<0.001

Correlation coefficients were calculated using Pearson's correlation analysis.

CI: confidence interval.

LDL: low-density lipoprotein

HDL: high-density lipoprotein

Changes following treatment with zinc histidine hydrate

Among the 54 patients who initiated treatment with zinc histidine hydrate, one discontinued treatment because of nausea, although a causal relationship with the medication could not be established.

Table 4 summarizes the laboratory parameters and darbepoetin doses before and after 3 months of treatment with zinc histidine hydrate (n = 53). Serum alkaline phosphatase (ALP) levels increased significantly from 79 ± 37 U/L to 87 ± 44 U/L (P = 0.004), and serum zinc concentrations increased significantly from 58 ± 9 μg/dL to 96 ± 37 μg/dL (P < 0.001). In contrast, serum copper concentrations decreased significantly from 95 ± 18 μg/dL to 86 ± 22 μg/dL (P < 0.001). No significant changes were observed in the other parameters.

Table 4. Changes in laboratory parameters and darbepoetin doses after 3 months of treatment with zinc histidine hydrate

Variable	Baseline	3 months	P value
Albumin (g/dL)	3.4 ± 0.4	3.5 ± 0.4	NS
Alkaline phosphatase (U/L)	79 ± 37	87 ± 44	0.004
C-Reactive protein (mg/dL)	0.48 ± 0.67	0.42 ± 0.87	NS
Transferrin saturation (%)	27.2 ± 10.2	26.7 ± 10.8	NS
Zinc (μg/dL)	58 ± 9	96 ± 37	<0.001
Copper (μg/dL)	95 ± 18	86 ± 22	<0.001
White blood cell count (/μL)	5900 ± 1700	6000 ± 1600	NS
Hemoglobin (g/dL)	10.8 ± 0.9	10.5 ± 0.9	NS
Platelet count ($x10^4$/μL)	18.1 ± 6.6	17.9 ± 6.2	NS
Darbepoetin dose (μg/week)	17 ± 14	18 ± 15	NS

Values are expressed as mean ± standard deviation.

NS, not statistically significant.

Discussion

In this study, 81.8% of patients undergoing maintenance hemodialysis had serum zinc concentrations below 80 μg/dL, including 23.4% with concentrations below 60 μg/dL. These findings indicate that low serum zinc concentrations were common in this population. Serum zinc levels were negatively correlated with serum copper and positively correlated with serum albumin. Furthermore, after 3 months of treatment with zinc histidine hydrate, serum zinc and ALP levels increased significantly ($P < 0.001$ and $P = 0.004$, respectively), whereas serum copper levels decreased significantly ($P < 0.001$).

Although few studies have evaluated the prevalence of zinc deficiency in maintenance hemodialysis patients, previous reports have shown that more than 90% of patients with chronic kidney disease or undergoing dialysis have hypozincemia [5, 7, 11]. The high prevalence of zinc deficiency in hemodialysis patients has been attributed to reduced dietary intake and zinc loss during dialysis [6]. Consistent with these findings, 81.8% of patients in the present study had serum zinc concentrations below 80 μg/dL.

Serum zinc levels were negatively correlated with serum copper and positively correlated with serum albumin. Zinc induces the expression of metallothionein in intestinal epithelial cells. Metallothionein has a higher affinity for copper than zinc, resulting in sequestration of copper within enterocytes. As intestinal epithelial cells are continuously shed into the intestinal lumen, copper absorption decreases and fecal copper excretion increases [12]. An inverse correlation between serum zinc and copper concentrations has previously been reported in patients undergoing dialysis [13, 14]. Therefore, clinicians

should be aware of the potential risk of copper deficiency during zinc supplementation. In contrast, Okamura et al. reported a significant positive correlation between serum zinc and albumin levels in hemodialysis patients (R = 0.55), and other studies have identified serum albumin as an independent determinant of serum zinc concentration [9, 15]. Because the majority of circulating serum zinc is bound to albumin, albumin serves as the principal transport protein for zinc, and reduced albumin concentrations may lead to lower serum zinc levels [16]. Furthermore, protein-energy wasting and chronic inflammation may reduce both albumin and zinc concentrations, thereby contributing to the observed positive correlation [17].

Zinc histidine hydrate, evaluated in the present study, forms a complex between zinc ions and histidine. This relatively stable complex is thought to release fewer zinc ions in the gastrointestinal tract than zinc acetate hydrate, potentially reducing direct gastrointestinal irritation. A recent randomized clinical trial reported numerically lower incidences of nausea and vomiting with zinc histidine hydrate than with zinc acetate hydrate, although the differences were not statistically significant [18].

To our knowledge, no previous studies have investigated the use of zinc histidine hydrate in patients undergoing maintenance hemodialysis. In the present study, only one of the 54 patients who initiated treatment (1.9%) discontinued treatment because of nausea, although a causal relationship with the medication could not be established. In contrast, a randomized controlled trial of zinc acetate hydrate reported gastrointestinal adverse events, including gastric discomfort, vomiting, diarrhea, and constipation, in 62.2% of patients [13]. These findings suggest that zinc histidine hydrate may be better tolerated than zinc acetate hydrate. However, the small sample size and the absence of a control group preclude definitive conclusions regarding the tolerability of zinc histidine hydrate. Direct comparative studies are needed to determine its relative tolerability compared with other zinc preparations.

Treatment with zinc histidine hydrate for 3 months significantly increased serum ALP levels. ALP is a zinc-dependent metalloenzyme that contains zinc ions at its catalytic active site. Zinc deficiency decreases ALP activity, whereas zinc supplementation restores enzymatic activity [19]. Previous studies have also reported increased ALP levels following zinc supplementation, and our findings are consistent with these observations [20]. Although ALP is a zinc-dependent enzyme, the clinical significance of this increase remains unclear. Because serum ALP levels may also be influenced by bone metabolism and hepatobiliary conditions, further studies are needed to clarify the significance of this finding in patients undergoing maintenance hemodialysis.

As expected, serum copper concentrations decreased following zinc supplementation. Zinc and copper competitively share intestinal absorption pathways, and prolonged oral zinc administration induces intestinal metallothionein, thereby reducing copper absorption. Therefore, careful monitoring for copper deficiency is recommended during long-term zinc therapy.

Previous studies have suggested that zinc supplementation may improve anemia and nutritional or inflammatory markers, including serum albumin and CRP concentrations [21, 22]. However, no statistically significant changes in these parameters were observed during the 3-month observation

period in our study. The relatively short follow-up period and the absence of a control group may have limited our ability to detect changes in these outcomes.

This study has several limitations. First, its retrospective observational design limits causal inference and may have introduced selection bias and confounding. Second, zinc deficiency-related clinical symptoms, including taste disturbances, were not systematically assessed. Third, the follow-up period was limited to 3 months, precluding evaluation of long-term efficacy and safety. Fourth, the study lacked a control group, and treatment was initiated at the discretion of the attending physician in patients who consented to treatment. Consequently, the observed changes cannot be attributed solely to zinc histidine hydrate. Finally, the relatively small treatment cohort limits the generalizability of the findings.

Conclusions

In this retrospective study of patients undergoing maintenance hemodialysis, treatment with zinc histidine hydrate for 3 months was associated with significant increases in serum zinc and ALP concentrations and a significant decrease in serum copper concentrations. One of the 54 patients who initiated treatment discontinued the medication because of nausea, although a causal relationship could not be established. These findings suggest that zinc histidine hydrate may be a treatment option for hypozincemia in patients undergoing maintenance hemodialysis. However, controlled studies with longer follow-up periods are needed to establish its clinical efficacy, long-term safety, and comparative tolerability.

Abbreviations

ALP: alkaline phosphatase

CRP: c-reactive protein

Declarations

Data availability

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Contributions

SOt conceived and designed the study, conducted the literature search, assessed the studies, extracted and analyzed the data, and drafted the manuscript. SOh, SOk, MB, NM, and TK were involved in the clinical management of hemodialysis patients with hypozincemia. All authors read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Sangenjaya hospital (approval No. R0801) and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants at the time of enrollment.

Consent for publication

Not applicable

Competing interest

The authors have no conflicts of interest to declare.

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