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ORIGINAL ARTICLE

Zinc deficiency is associated with erythropoietin-stimulating agents hyporesponsive anemia in peritoneal dialysis patients: a cross-sectional study

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Abstract

Background Zinc deficiency is widely recognized as a cause of anemia, but no studies have clarified the impact of zinc deficiency on achieving target hemoglobin levels in patients undergoing peritoneal dialysis (PD) and receiving high-dose erythropoiesis-stimulating agent (ESA) therapy. This study aimed to investigate the relationship between zinc deficiency and ESA-hyporesponsive anemia in patients on PD.

Methods This cross-sectional study included 164 patients on PD aged ≥ 18 years. The target hemoglobin level was 11–13 g/dL. ESA dosage was categorized as low-dose (< 120 μg/month) or high-dose (≥ 120 μg/month), while zinc deficiency was defined as a serum zinc level < 60 μg/dL. A logistic regression model was used to calculate the odds ratio (OR) for achieving the target hemoglobin level.

Results The proportion of patients achieving the target hemoglobin level was 48.2% in the low-dose ESA and non-zinc-deficient group, and 12.2% in the high-dose ESA and zinc-deficient group. Compared with the low-dose ESA and non-zinc-deficient group, the adjusted OR for achieving the target hemoglobin level was significantly lower in the high-dose ESA and zinc-deficient group (OR: 0.19, 95% confidence interval 0.05–0.72). Stratified analyses based on serum albumin, serum C-reactive protein, and transferrin saturation did not change the association between the high-dose ESA and zinc-deficient group and the achievement of the target hemoglobin level.

Conclusion Zinc deficiency in patients on PD is a significant barrier to achieving the target hemoglobin level, and serum zinc levels should be routinely monitored in patients with ESA-hyporesponsive anemia.

Keywords Zinc deficiency · Peritoneal dialysis · Anemia · ESA hyporesponsiveness · Erythropoietin · Nutritional deficiency

Introduction

Renal anemia is one of the major complications in patients on dialysis and is known to cause fatigue, reduced exercise tolerance, depression, and dyspnea, significantly impairing the patient's quality of life [1, 2]. Furthermore, anemia is associated with increased incidence and mortality of cardiovascular disease [3]. The introduction of erythropoiesis-stimulating agents (ESAs) has radically improved anemia management in patients on dialysis. However, patients who are hyporesponsive to ESAs require high doses to achieve target hemoglobin levels. A reduced response to ESAs is associated with increased healthcare costs [4], a higher risk of thrombosis, and elevated incidence and mortality of cardiovascular disease [5–7]. Therefore, identifying modifiable risk factors for ESA hyporesponsiveness is crucial for

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optimizing anemia management. Several factors are known to contribute to poor ESA responsiveness, including iron deficiency, inflammation, hyperparathyroidism, bleeding, and reduced residual kidney function [8, 9]. The potential involvement of nutritional deficiencies, such as vitamin B12, folic acid, carnitine, and zinc, is receiving increasing attention [10–12].

Zinc is an essential trace element required for enzyme activation and is involved in various biological processes, including cell division, nucleic acid metabolism, cellular metabolism, growth, tissue repair, neurotransmitter synthesis, and inflammation. As a result, zinc deficiency has a wide range of health effects, such as anemia, dermatitis, taste disorders, impaired wound healing, osteoporosis, and gastrointestinal symptoms [13]. Recent studies in patients on hemodialysis (HD) suggest that zinc deficiency may impair erythropoiesis and exacerbate poor ESA responsiveness [14, 15]. However, while the association between zinc deficiency and ESA hyporesponsiveness has been reported in these patients, the prevalence of zinc deficiency in patients on peritoneal dialysis (PD) and its impact on ESA responsiveness remain largely unexplored. Differences in dialysis modalities between PD and HD may result in distinct patterns of trace element loss, suggesting that the mechanisms underlying zinc deficiency could differ.

In this study, we aimed to investigate the relationship between zinc deficiency and ESA-hyporesponsive anemia in patients undergoing PD. The rationale was to determine whether zinc deficiency is an independent risk factor for ESA hyporesponsiveness in patients undergoing PD.

Materials and methods

Study population

This cross-sectional study included 164 patients on PD who attended monthly outpatient visits at Kokura Memorial Hospital between May and November 2020. The inclusion criteria were patients aged ≥ 18 years who had been undergoing PD for at least 3 months prior to the beginning of the study. The use of ESAs was not a mandatory requirement. Patients who met any of the following criteria were excluded from the study: hematological disorders, such as aplastic anemia or myelodysplastic syndrome; a history of acute bleeding within 3 months prior to enrollment; and chronic wasting diseases, such as active malignancies or severe heart failure. Patients were recruited through a convenience sampling method.

This study was conducted in accordance with the declaration of Helsinki and was approved by the Ethics Committee of Kokura Memorial Hospital (Approval No.: 24122401). Given the retrospective nature of the study, informed consent was obtained using an opt-out approach. Specifically, details of the study were made publicly available on the hospital's website, allowing patients the opportunity to decline participation.

Methodology

At Kokura Memorial Hospital, the treatment of renal anemia in all patients on dialysis follows the 2015 Japanese Society for Dialysis Therapy Guidelines for the treatment of renal anemia in chronic kidney disease [16]. The target hemoglobin level was set at 11–13 g/dL. ESA therapy is administered and adjusted to maintain hemoglobin levels within this target range, with the dosage modified according to the most recent hemoglobin measurement obtained during outpatient visits.

Patients receive erythropoiesis-stimulating agents as either darbepoetin alfa or epoetin beta pegol. Doses of darbepoetin alfa and epoetin beta pegol are treated as dose-equivalent at a 1:1 ratio [5]. No hypoxia-inducible factor prolyl hydroxylase inhibitors are used during the study period.

The average ESA dosage at our institution is 113 μg/month. Based on the dosage, patients were categorized into low-dose ESA (< 120 μg/month) and high-dose ESA (≥ 120 μg/month) groups. Serum zinc levels were classified according to the criteria of the Japanese society of clinical nutrition [13], defining zinc deficiency as < 60 μg/dL and non-deficiency as ≥ 60 μg/dL.

Furthermore, based on ESA dosage and serum zinc levels, patients were classified into the following 4 groups: patients receiving ESA < 120 μg/month and serum zinc ≥ 60 μg/dL, patients receiving ESA < 120 μg/month and serum zinc < 60 μg/dL, patients receiving ESA ≥ 120 μg/month and serum zinc ≥ 60 μg/dL, and patients receiving ESA ≥ 120 μg/month and serum zinc < 60 μg/dL.

Clinical course parameters

Blood samples were collected during routine monthly outpatient visits, and the timing of blood collection varied among individuals. Clinical parameters, including age, sex, PD vintage, body mass index, and the presence of diabetes, were obtained from the medical records. Medication data included the use of phosphate binders, proton pump inhibitors, oral iron supplements, and oral zinc supplements. Laboratory parameters included levels of erythropoietin, hemoglobin, serum albumin, blood urea nitrogen, creatinine, C-reactive protein (CRP), zinc, iron, transferrin saturation (TSAT), ferritin, and total cholesterol. Dialysis efficiency was assessed using dialysis indices, including total Kt/V urea and renal Kt/V urea.

Data analysis

Baseline characteristics are summarized using mean ± standard deviation or median [IQR], as appropriate, for continuous variables, and number (percentage) for categorical variables. Among the 4 groups classified based on ESA dosage and serum zinc levels, continuous variables were compared using the Kruskal–Wallis test, and categorical variables were compared using the chi-square test. Logistic regression analysis was performed to calculate the odds ratio (OR) for achieving the target hemoglobin level (11–13 g/dL), adjusting for age, sex, PD vintage, serum albumin, serum CRP, TSAT, and total Kt/V for urea. Because dividing the low-ESA group by zinc status resulted in sparse data that were not suitable for reliable statistical analysis, stratified analyses were performed using a 3-group classification consisting of the low-ESA group, the high-ESA and non-zinc-deficient group, and the high-ESA and zinc-deficient group, to evaluate potential confounding factors including serum albumin, serum CRP, and TSAT. The erythropoietin resistance index (ERI) was calculated by dividing the weekly weight-adjusted ESA dose by the hemoglobin concentration (g/dL) [17]. The relationship between ERI and serum zinc levels was analyzed using linear regression analysis.

A p value of < 0.05 was considered statistically significant. All statistical analyses were performed using JMP version 18 (SAS Institute Inc.).

Results

Table 1 presents a comparison of all study participants and the four groups according to ESA dosage and serum zinc levels. The overall mean age was 67.4 ± 11.7 years. PD vintage was 44.0 [28.3–66.8] months, and serum zinc was 59.0 [52.0–68.0] μg/dL. In the overall cohort, 51.2% of patients had zinc deficiency (serum zinc < 60 μg/dL). Renal Kt/V ($p = 0.003$) significantly decreased with an increase in ESA dosage and a decline in serum zinc levels. Serum albumin ($p < 0.001$), serum iron ($p = 0.01$), and TSAT ($p = 0.003$) also differed among groups.

Figure 1 shows the proportion of patients achieving the target hemoglobin level. The achievement rates were 48.2% in the ESA < 120 μg/month and serum zinc ≥ 60 μg/dL group, 48.8% in the ESA < 120 μg/month and serum zinc < 60 μg/dL group, 41.7% in the ESA ≥ 120 μg/month and serum zinc ≥ 60 μg/dL group, and 12.2% in the ESA ≥ 120 μg/month and serum zinc < 60 μg/dL group. The achievement rate significantly decreased with a higher ESA dosage and lower serum zinc levels ($p = 0.001$).

Table 2 shows the ORs for achieving the target hemoglobin level in each group. Compared with the ESA < 120 μg/month and serum zinc ≥ 60 μg/dL group, the sex and age-adjusted OR for achieving the target hemoglobin level in the ESA ≥ 120 μg/month and serum zinc < 60 μg/dL group was 0.15 (95% confidence interval [CI] 0.04–0.40), showing a significant decrease. Even after further adjustment for PD vintage, serum albumin, serum CRP, TSAT, and total Kt/V in addition to age and sex, the multivariable-adjusted OR remained significantly lower at 0.19 (95% CI 0.05–0.72).

We conducted stratified analyses (Table 3) using the ESA < 120 μg/month group as the reference category, adjusting for serum albumin (A), serum CRP (B), and TSAT (C), which might affect the relationship between ESA dosage, serum zinc levels, and achievement of the target hemoglobin level.

Among patients with serum albumin ≥ 3 g/dL, the multivariable-adjusted OR for achieving the target hemoglobin level in the ESA ≥ 120 μg/month and serum zinc < 60 μg/dL group, compared with the ESA < 120 μg/month group, was 0.13 (95% CI 0.03–0.54). Similarly, in patients with serum albumin < 3 g/dL, the multivariable-adjusted OR was 0.05 (95% CI 0.002–1.16), indicating a significant decrease in both subgroups. Stratified analysis by serum CRP levels (≥ 0.3 mg/dL vs. < 0.3 mg/dL) also showed that the multivariable-adjusted ORs for achieving the target hemoglobin level in the ESA ≥ 120 μg/month and serum zinc < 60 μg/dL group were 0.39 (95% CI 0.08–2.01) and 0.15 (95% CI 0.04–0.66), for the 2 CRP groups, respectively, both demonstrating a significant decrease. Similarly, in the stratified analysis by TSAT (≥ 30% vs. < 30%), the ORs were 0.29 (95% CI 0.08–1.11) and < 0.001 (95% CI 0–0.001), respectively, showing consistent results. No clear evidence of heterogeneity was detected across subgroups defined by serum albumin, serum CRP, and TSAT. Furthermore, no difference was observed in the association between low serum zinc levels and ESA hyporesponsiveness across the subgroups.

In addition, we examined the relationship between serum zinc levels and ERI (Fig. 2). A significant linear relationship was observed, with ERI increasing as serum zinc levels decreased ($r = -0.25$, $p = 0.001$).

Discussion

To the best of our knowledge, this study is the first to investigate the relationship between zinc deficiency and ESA hyporesponsiveness in patients undergoing PD. Our findings revealed a high prevalence of zinc deficiency in these patients, with 51.2% of patients having serum zinc levels < 60 μg/dL. In the 4-group analysis based on ESA dosage and serum zinc levels, patients receiving high-dose ESA with zinc deficiency showed the lowest likelihood of achieving the target hemoglobin level. Furthermore, this association remained consistent in stratified analyses

Table 1 Clinical characteristics of patients grouped by ESA levels and serum zinc levels

	All patients	ESA < 120 μg/month		ESA ≥ 120 μg/month		p value
		zinc ≥ 60 μg/dL	zinc < 60 μg/dL	zinc ≥ 60 μg/dL	zinc < 60 μg/dL	
	n = 164	*n* = 56	*n* = 43	*n* = 24	*n* = 41	
Age, years	67.4 (11.7)	67.4 (10.4)	70.5 (12.3)	61.5 (11.9)	67.6 (11.6)	0.02*
Male, *n* (%)	116 (70.7)	39 (69.6)	31 (72.1)	18 (75.0)	28 (68.3)	0.94
Peritoneal dialysis vintage, months	44.0 [28.3–66.8]	35.0 [26.3–53.5]	48.0 [31.0–71.0]	52.5 [28.3–84.3]	47.0 [29.0–74.5]	0.04*
Diabetes, *n* (%)	90 (54.9)	32 (57.1)	21 (48.8)	17 (70.8)	20 (48.8)	0.28
Systolic blood pressure, mmHg	136.3 (23.5)	133.6 (22.2)	128.8 (19.3)	147.0 (24.5)	141.9 (25.8)	0.006*
Diastolic blood pressure, mmHg	72.5 (15.4)	72.2 (13.6)	69.6 (15.9)	77.5 (14.4)	73.0 (17.4)	0.38
Body mass index, kg/m^2	24.9 (4.0)	24.9 (3.9)	23.7 (3.5)	26.9 (5.2)	25.1 (3.7)	0.03*
Hemoglobin, g/dL	10.8 (1.2)	11.2 (1.0)	11.0 (1.2)	10.6 (1.2)	10.0 (1.1)	< 0.001*
Serum albumin, g/dL	3.2 (0.4)	3.4 (0.3)	3.0 (0.41)	3.3 (0.5)	3.0 (0.4)	< 0.001*
Serum blood urea nitrogen, mg/dL	56.4 (12.8)	54.9 (11.3)	56.4 (14.0)	56.6 (12.0)	58.3 (13.9)	0.50
Serum creatinine, mg/dL	11.0 (7.8)	12.2 (12.6)	9.7 (3.2)	11.2 (2.6)	10.7 (3.0)	0.06
Serum CRP, mg/dL	0.2 [0.1–0.8]	0.1 [0.1–0.4]	0.2 [0.1–1.0]	0.2 [0.1–0.7]	0.3 [0.1–1.1]	0.47
Serum zinc, μg/dL	59.0 [52.0–68.0]	68.0 [63.3–74.8]	54.0 [49.0–57.0]	68.5 [63.3–75.3]	51.0 [45.0–54.5]	< 0.001*
Zinc deficiency, *n* (%)	84 (51.2)	0 (0.0)	43 (100.0)	0 (0.0)	41 (100.0)	< 0.001*
Serum iron, μg/dL	80.0 [63.0–95.8]	84.5 [73.3–103.5]	81.0 [68.0–94.0]	68.0 [43.3–88.3]	75.0 [55.5–101.5]	0.01*
Transferrin saturation, %	35.0 (14.1)	37.5 (11.4)	35.8 (13.8)	26.6 (9.5)	35.9 (18.2)	0.003*
Serum ferritin, ng/mL	184.4 [93.6–321.9]	202.7 [122.5–376.4]	193.1 [99.6–298.8]	132.4 [56.6–284.1]	149.8 [79.9–274.7]	0.06
Serum total cholesterol, mg/dL	171.1 (39.2)	178.5 (44.7)	178.5 (38.1)	155.3 (34.3)	162.6 (31.0)	0.03*
Total Kt/V for urea	1.47 [1.32–1.66]	1.51 [1.36–1.70]	1.49 [1.32–1.64]	1.47 [1.33–1.66]	1.40 [1.23–1.57]	0.15
Renal Kt/V for urea	0.30 [0.07–0.59]	0.41 [0.21–0.67]	0.28 [0.11–0.59]	0.29 [0.02–0.50]	0.09 [0.04–0.39]	0.003*
Use of phosphate binders, *n* (%)	123 (75.0)	41 (73.2)	28 (65.1)	20 (83.3)	34 (82.9)	0.20
Use of proton pump inhibitors, *n* (%)	73 (44.5)	29 (51.8)	20 (46.5)	10 (41.7)	14 (34.1)	0.37
Use of iron supplementation, *n* (%)	51 (31.1)	23 (41.1)	10 (23.3)	4 (16.7)	14 (34.1)	0.10
Use of zinc supplementation, *n* (%)	8 (4.9)	1 (1.8)	1 (2.3)	5 (20.8)	1 (2.4)	0.004*
Use of darbepoetin alfa, *n* (%)	51 (31.1)	16 (28.6)	12 (27.9)	5 (20.8)	18 (43.9)	0.20
Use of epoetin beta pegol, *n* (%)	91 (55.5)	26 (46.4)	23 (53.5)	19 (79.2)	23 (56.1)	0.06
Dose of ESA, μg/month	112.7 (83.2)	52.1 (37.6)	57.7 (35.1)	209.2 (53.6)	196.6 (46.4)	< 0.001*
ERI, IU/week/kg/g/dL	8.5 (6.8)	3.6 (2.7)	4.5 (3.0)	14.6 (5.5)	15.7 (5.0)	< 0.001*

Values are expressed as mean (SD), median [IQR], or number (percentage), as appropriate

*p value < 0.05 was considered statistically significant

CRP C-reactive protein, *ESA* erythropoiesis-stimulating agent, *ERI* erythropoietin resistance index

using the low-dose ESA group as the reference category across subgroups defined by serum albumin, serum CRP, and TSAT. In addition, the observed negative correlation between ERI and zinc levels supports the potential involvement of zinc deficiency in ESA hyporesponsiveness.

The impact of zinc deficiency on ESA-hyporesponsive anemia can be explained by the following 3 potential mechanisms: (1) inhibition of erythropoiesis due to zinc deficiency, (2) shortened red blood cell lifespan caused by increased erythrocyte fragility, and (3) impaired erythropoietin

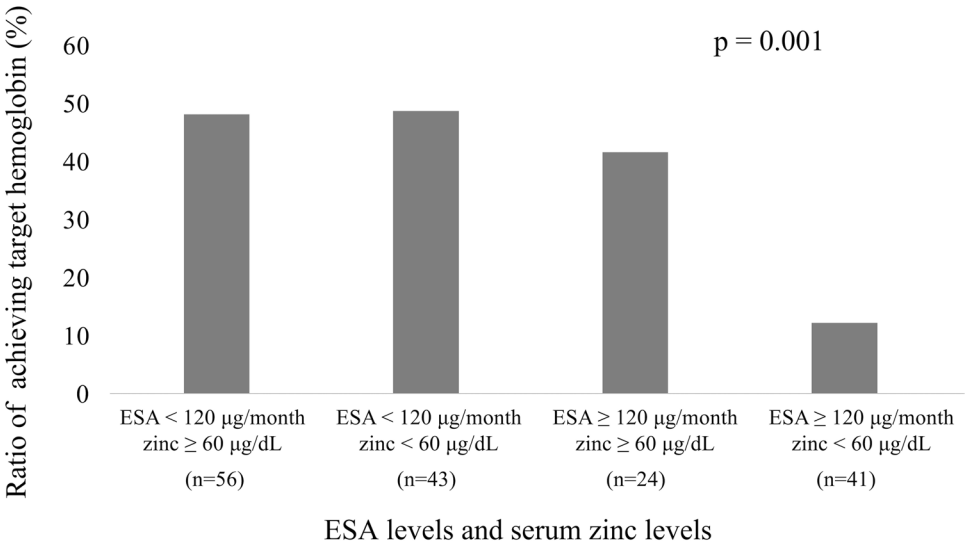

Fig. 1 Ratio of achieving target hemoglobin by ESA levels and serum zinc levels. p values were calculated using the chi-square test. *ESA* erythropoiesis stimulating agent

Table 2 Odds ratio for achieving target hemoglobin by ESA levels and serum zinc levels

	Number of achievements	Number of subjects	Model 1		Model 2	
			OR (95%CI)	p value	OR (95%CI)	p value
ESA levels and serum zinc levels						
ESA < 120 μg/month zinc ≥ 60 μg/dL	27	56	1.00 (references)		1.00 (references)	–
ESA < 120 μg/month zinc < 60 μg/dL	21	43	0.99 (0.44–2.23)	0.98	1.67 (0.60–4.65)	0.32
ESA ≥ 120 μg/month zinc ≥ 60 μg/dL	10	24	0.77 (0.28–2.06)	0.60	0.77 (0.24–2.48)	0.66
ESA ≥ 120 μg/month zinc < 60 μg/dL	5	41	0.15 (0.04–0.40)	< 0.001*	0.19 (0.05–0.72)	0.02*

Model 1: age and sex; Model 2: Model 1 + PD vintage, serum albumin, serum CRP, transferrin saturation, and total Kt/V for urea

*p < 0.05 was considered statistically significant

OR odds ratio, *CI* confidence interval, *ESA* erythropoiesis-stimulating agent, *PD* peritoneal dialysis

production caused by zinc deficiency. Zinc is an essential trace element involved in hematopoiesis, and its deficiency may impair erythropoiesis. Zinc finger proteins, which contain zinc, are crucial for erythroblast differentiation and proliferation, and zinc deficiency disrupts this process [13]. In addition, zinc plays a role in maintaining erythrocyte membrane stability, and thus zinc deficiency may increase membrane fragility, making red blood cells more susceptible to hemolysis, particularly in patients on HD exposed to mechanical stress during dialysis [16, 18]. Furthermore, although no definitive conclusions have been drawn in humans, findings in animal models show that zinc deficiency may reduce erythropoietin production [19, 20]. In the present study, the lower rate of achieving the target hemoglobin level in the high-dose ESA and zinc-deficient group suggests that zinc deficiency may contribute to impaired erythropoiesis and serve as a risk factor for ESA hyporesponsiveness.

Zinc deficiency is prevalent in patients receiving either HD or PD. A cross-sectional study of Japanese patients on dialysis reported that 70.2% of those on HD and 59.6% of those on PD had clinical zinc deficiency (serum zinc level < 60 μg/dL), with no significant difference between the 2 groups [21]. This finding is consistent with our results, in which 51.2% of patients on PD had serum zinc levels below this threshold, further suggesting a high prevalence of zinc deficiency in these patients.

Zinc deficiency in dialysis patients is caused by several factors, including dietary restrictions, insufficient protein intake, reduced gastrointestinal zinc absorption, urinary protein loss, and increased zinc utilization due to inflammation [21–23]. These factors are common to patients on HD or PD, although zinc loss differs according to the dialysis modality. During HD, zinc is removed through the dialysis membrane, leading to zinc loss as a direct consequence of the

Table 3 Odds ratio for achieving target hemoglobin by ESA levels and serum zinc levels stratified by (A) serum albumin level (≥ 3.0 and < 3.0 g/dL), (B) serum CRP level (≥ 0.3 and < 0.3 mg/dL), and (C) TSAT (≥ 30 and < 30%)

(A) ESA levels and serum zinc levels	Number of achievements	Number of subjects	Model 1			Model 2		
			OR (95% CI)	p value	p for heterogeneity	OR (95% CI)	p value	p for heterogeneity
serum albumin ≥ 3.0 g/dL								
ESA < 120 μg/month	37	75	1.00 (references)	–	0.94	1.00 (references)	–	0.92
ESA ≥ 120 μg/month zinc ≥ 60 μg/dL	8	19	0.74 (0.26–2.14)	0.58		0.58 (0.16–2.08)	0.40	
ESA ≥ 120 μg/month zinc < 60 μg/dL	3	26	0.13 (0.04–0.47)	0.002*		0.13 (0.03–0.54)	0.005*	
serum albumin < 3.0 g/dL								
ESA < 120 μg/month	11	24	1.00 (references)	–		1.00 (references)	–	0.92
ESA ≥ 120 μg/month zinc ≥ 60 μg/dL	2	5	1.23 (0.15–10.4)	0.85		0.61 (0.03–12.75)	0.75	
ESA ≥ 120 μg/month zinc < 60 μg/dL	2	15	0.19 (0.03–1.06)	0.06		0.05 (0.002–1.16)	0.06	
(B) ESA levels and serum zinc levels	Number of achievements	Number of subjects	Model 1			Model 2		
			OR (95% CI)	p value	p for heterogeneity	OR (95% CI)	p value	p for heterogeneity
serum albumin ≥ 3.0 g/dL								
ESA < 120 μg/month	15	41	1.00 (references)	–	0.56	1.00 (references)	–	0.76
ESA ≥ 120 μg/month zinc ≥ 60 μg/dL	5	11	1.06 (0.25–4.53)	0.94		1.03 (0.18–5.90)	0.98	
ESA ≥ 120 μg/month zinc < 60 μg/dL	2	21	0.16 (0.03–0.83)	0.03*		0.39 (0.08–2.01)	0.26	
serum albumin < 3.0 g/dL								
ESA < 120 μg/month	31	53	1.00 (references)	–	0.56	1.00 (references)	–	0.76
ESA ≥ 120 μg/month zinc ≥ 60 μg/dL	5	13	0.41 (0.11–1.52)	0.18		0.48 (0.12–1.90)	0.30	
ESA ≥ 120 μg/month zinc < 60 μg/dL	2	17	0.09 (0.02–0.43)	0.003*		0.15 (0.04–0.66)	0.01*	
(c) ESA levels and serum zinc levels	Number of achievements	Number of subjects	Model 1			Model 2		
			OR (95% CI)	p value	p for heterogeneity	OR (95% CI)	p value	p for heterogeneity
transferrin saturation ≥ 30%								
ESA < 120 μg/month	35	73	1.00 (references)	–	0.43	1.00 (references)	–	0.07
ESA ≥ 120 μg/month zinc ≥ 60 μg/dL	3	9	0.56 (0.12–2.54)	0.45		0.44 (0.08–2.52)	0.36	
ESA ≥ 120 μg/month zinc < 60 μg/dL	4	23	0.23 (0.07–0.71)	0.01*		0.29 (0.08–1.11)	0.07	
serum albumin < 3.0 g/dL								
ESA < 120 μg/month	13	26	1.00 (references)	–	0.43	1.00 (references)	–	0.07
ESA ≥ 120 μg/month zinc ≥ 60 μg/dL	7	15	0.99 (0.26–3.79)	0.99		0.47 (0.06–3.52)	0.46	
ESA ≥ 120 μg/month zinc < 60 μg/dL	1	18	0.06 (0.01–0.50)	0.01*		< 0.001(0–0.001)	0.99	

Model 1: age and sex; Model 2: Model 1+PD vintage, serum albumin, serum CRP, transferrin saturation, and total Kt/V for urea. We excluded the factor used for stratification from the covariates in the model

*p < 0.05 was considered statistically significant for both the main analysis and for heterogeneity

OR odds ratio, *CI* confidence interval, *ESA* erythropoiesis stimulating agent, *CRP* C-reactive protein

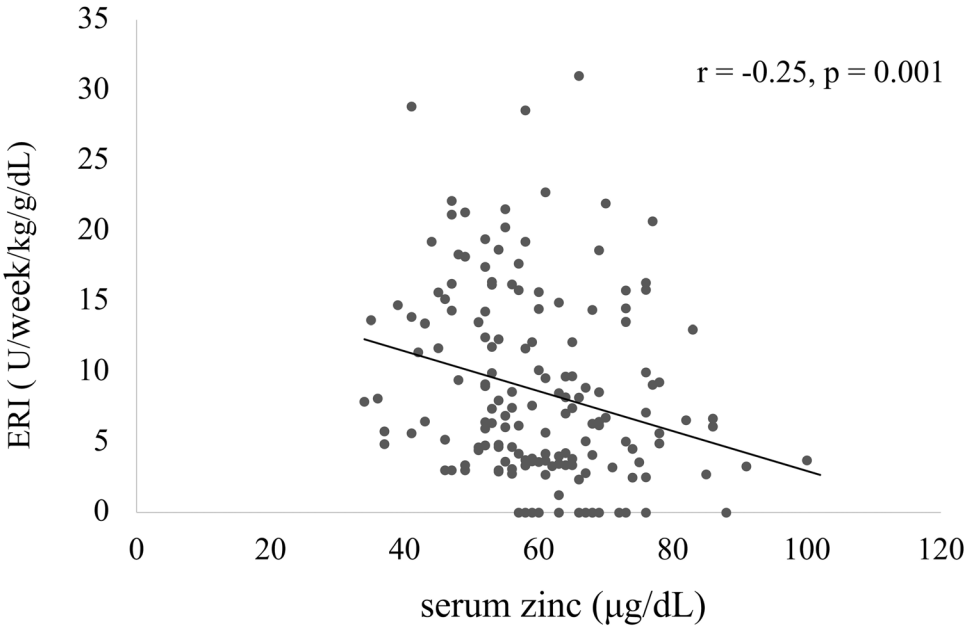

Fig. 2 Relationship between ERI and serum zinc levels. *ERI* erythropoietin resistant index

dialysis procedure [22]. In contrast, zinc loss to the dialysis fluid has been suggested in PD. Although PD is reported to cause minimal zinc loss [23], recent research has shown that protein loss during PD correlates with a decrease in serum zinc levels, suggesting the possibility of protein-bound zinc loss [24]. However, the extent to which PD effluent contributes to zinc loss remains inconclusive, necessitating further investigation.

The present study findings suggest that zinc deficiency may be a risk factor for ESA-hyporesponsive anemia in patients on PD. Despite the high prevalence of zinc deficiency in these patients, serum zinc monitoring is not routinely performed in clinical practice. Iron deficiency and inflammation are widely recognized as the most common factors contributing to ESA hyporesponsiveness [25]; however, our findings indicate that the role of zinc should also be considered. In particular, for patients undergoing PD requiring high doses of ESA, regular assessment of serum zinc levels should be incorporated into anemia management. If zinc deficiency is detected, appropriate supplementation should be considered. Since this study was a cross-sectional analysis and did not directly evaluate the effect of zinc supplementation on ESA responsiveness in the patients, future interventional studies should investigate whether zinc supplementation can help improve ESA hyporesponsiveness.

This study has several limitations. First, as a retrospective cross-sectional study, a causal relationship between zinc deficiency and ESA-hyporesponsive anemia could not be established. Although patients receiving high-dose ESA with zinc deficiency had a lower rate of achieving the target hemoglobin level, it remains unclear whether this was due to zinc deficiency impairing erythropoiesis or whether anemia progression led to increased zinc utilization for erythropoiesis, thereby reducing serum zinc levels. The association between zinc deficiency and ESA hyporesponsiveness has already been established in patients on HD, but it remains uncertain whether a similar relationship exists in patients on PD. Further prospective interventional studies are needed to evaluate the effect of zinc supplementation on ESA responsiveness in this population. Second, this study was conducted at a single center with a relatively small sample size. Nevertheless, the treatment protocol for patients on PD was standardized, and blood sampling conditions and measurement methods were consistent, ensuring the reliability of the data. Third, serum zinc levels were not measured at a uniform time point. As dietary intake is known to influence serum zinc levels [26], we cannot rule out the possibility that timing differences may have affected the results. Nonetheless, differences in measurement times could not weaken the impact of low serum zinc levels on ESA hyporesponsiveness and are unlikely to have biased the study findings. Fourth, we defined ESA hyporesponsiveness as ESA $\geq$ 120 μg/month, which is slightly lower than the threshold suggested in existing guidelines [16]. Therefore, some patients in our study may have been classified as ESA-hyporesponsive due to inadequate ESA dosing. Fifth, serum zinc levels were used as an indicator of zinc deficiency, yet zinc is primarily distributed intracellularly within bones and muscles. Thus, it remains uncertain whether serum zinc levels accurately reflect total body zinc status. Finally, this study did not measure other nutrients, such as copper and carnitine, which may also influence anemia. The potential impact of these confounding factors could not be evaluated. Future prospective studies that address these limitations are

warranted to further clarify the relationship between zinc deficiency and ESA hyporesponsiveness.

Conclusion

This study revealed that zinc deficiency is highly prevalent in patients undergoing PD and is independently associated with ESA hyporesponsiveness. Given this association, regular monitoring of zinc levels and appropriate supplementation should be considered part of anemia management in patients on PD requiring high-dose ESA. Further prospective interventional studies are needed to determine whether zinc supplementation can enhance ESA responsiveness and optimize anemia treatment in patients on PD.

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Data availability The data that support the findings of this study are not publicly available due to privacy concerns.

Declarations

conflict of interest The authors have declared that no conflict of interest exists.

Informed consent Given the retrospective nature of the study, informed consent was obtained using an opt-out approach. Specifically, details of the study were made publicly available on the hospital's website, allowing patients the opportunity to decline participation.

Research involving Human Participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Kokura Memorial Hospital (IRB approval number 24122401) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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