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Keywords: zinc deficiency; prevalence; predictive factor



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Article

Prevalence and Predictive Factors of Zinc Deficiency in Orthopaedic Inpatients

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Abstract: Zinc, an essential trace mineral, plays a crucial role in over 300 enzymes that are vital for major metabolic pathways. Zinc deficiency can cause various symptoms and sometimes lead to serious conditions, especially after surgery. Therefore, recognising the prevalence and predictors of zinc deficiency before surgery is essential for preventing associated symptoms. Although zinc deficiency is linked to several diseases, its association with orthopaedic disorders remains unclear. This retrospective study aimed to explore the prevalence and predictors of zinc deficiency in orthopaedic inpatients prior to surgery. This retrospective case-control study aimed to investigate the prevalence and predictors of zinc deficiency in orthopaedic inpatients. Patients admitted to the Department of Orthopaedic Surgery at Teikyo University Chiba Medical Center between 15 February 2022 and 31 August 2022 were included. The case-control design categorised patients into zinc deficiency (case) and non-deficiency (control) groups based on serum zinc concentrations ($< 60 \mu\text{g/dL}$). The data retrieved from the centre's database included demographics, comorbidities, reasons for hospitalisation, fracture details, medication use, and laboratory values. Statistical tests included Fisher's exact test for categorical variables and a two-sample t-test for continuous variables. To identify factors associated with zinc deficiency, multivariate analysis (backward stepwise regression model) was performed for items that were significantly different from the univariate analysis. A total of 156 orthopaedic patients were included in this study. Forty-seven patients (30.1%) had a zinc deficiency. The fracture rate was significantly higher in the case group than in the control group (68.1% vs. 33.9%; $p < 0.001$); spinal disease was significantly less common in the case group than in the control group (2.1% vs. 31.2%; $p < 0.001$); and OA was significantly less common in the case group than in the control group (8.5% vs. 22.9%; $p = 0.04$). The case group had significantly higher rates of fragility and hip and pelvic fractures than did the control group. Spinal disease was less common in the case group than in the control group. Laboratory findings revealed significantly lower mean serum zinc ($46.2 \mu\text{g/dL}$) in the case group than in the control group ($76.3 \mu\text{g/dL}$), accompanied by lower albumin and haemoglobin concentrations. Hypoalbuminemia and anaemia were more prevalent in the case group than in the control group. Multivariate logistic regression identified age ≥ 60 , anaemia, hip fracture, and hypoalbuminaemia as independent predictive factors for zinc deficiency, while spinal disease was associated with decreased risk. This study identified zinc deficiency in 30.1% of orthopaedic inpatients based on serum zinc concentrations. Furthermore, age ≥ 60 , anaemia, hip fracture, and hypoalbuminaemia were determined as independent predictive factors for zinc deficiency.

Keywords: zinc deficiency; prevalence; predictive factor

1. Introduction

Zinc is a nutritionally essential trace mineral required for the activity of more than 300 enzymes involved in major metabolic pathways [1]. It is distributed throughout the body, with 85% located in muscles and bones, 11% in the skin and liver, and the remainder in other tissues [1]. A zinc deficiency is known to cause a variety of symptoms, including skin disorders [2], taste disorders [3], gonadal

dysfunction in men [4], loss of appetite [5], diarrhoea [6,7], delayed wound healing [8,9], and increased susceptibility to infection [10]. These symptoms can lead to serious complications, particularly postoperatively. For instance, a prospective 15-month study of 80 consecutive patients undergoing total hip arthroplasty (THA) demonstrated an association between zinc deficiency and delayed wound healing in THA patients [8]. Another prospective study of 97 patients undergoing hip hemiarthroplasty for hip fractures concluded that serum zinc levels predicted delayed wound healing [9]. Notably, delayed wound healing after hemiarthroplasty or THA not only increases the risk of prosthetic infection [11,12] but may also extend hospital stay [13] and increase healthcare costs [14].

Understanding the prevalence and predictive factors of zinc deficiency before surgery is valuable for preventing symptoms arising from it. Furthermore, zinc deficiency has been linked to conditions such as cirrhosis [15,16], diabetes [17], chronic inflammatory bowel disease [18], and chronic kidney disease [19]. However, its association with orthopaedic disorders remains unclear. Additionally, the prevalence and predictive factors for zinc deficiency in orthopaedic inpatients before surgery are not well known. To address these concerns, we conducted a retrospective study to examine the prevalence and predictors of zinc deficiency in hospitalised patients.

2. Materials and Methods

2.1. Patient selection

The study included patients admitted to the Department of Orthopedic Surgery of Teikyo University Chiba Medical Center between 15 February 2022 and 31 August 2022. The exclusion criteria were as follows: (1) patients whose zinc level was not measured during routine tests on admission, (2) patients who had previously been diagnosed with zinc deficiency, and (3) patients who were receiving zinc supplementation.

2.2. Study Design

The study used a case-control design, with patients with zinc deficiency included in the case group and those without zinc deficiency included in the control group. In this study, serum zinc concentration served as the primary marker for assessing zinc deficiency, given its widespread use and availability as an indicator of zinc deficiency risk [20–23]. Zinc deficiency was characterized by a serum zinc concentration of less than 60 µg/dL, in accordance with the treatment guidelines for zinc deficiency as published by the Japanese Society of Clinical Nutrition [24]. Serum samples were obtained at the time of admission. This study was approved by the Institutional Review Board of Teikyo University, IRB No.23-038). Because this was a retrospective study, the requirement for informed consent was waived.

2.3. Data collection

The data used in this study were retrieved from the computerised database of Teikyo University Chiba Medical Center. The following data were retrieved from the patient records: demographics (gender, age, height, weight, body mass index [BMI]), comorbidity (diabetes mellitus, hypothyroidism, gastroesophageal reflux disease, depression, haemodialysis), the reason for hospitalization, details of fractures, medication use (zinc, iron, magnesium, Vitamin D, and calcium supplements, proton pump inhibitors, H2 receptor antagonists, diuretics, antihypertensive, opioid, and antibiotics), and laboratory data (zinc, calcium, albumin, creatine, estimated glomerular filtration rate, haemoglobin, haemoglobin A1c, and alkaline phosphatase).

2.4. Statistics

Means with standard deviations (SD) and percentages were used to report continuous and categorical variables, respectively. Statistical analyses were performed using Fisher's exact test for categorical variables and a two-sample t-test for continuous variables. To identify factors associated with zinc deficiency, multivariate analysis (backward stepwise regression model) was performed for

items that were significantly different from the univariate analysis. All p values were two-sided, and p values less than 0.05 were considered statistically significant. All statistical analyses were performed using EZR version 1.52 [25], which is a graphical user interface for R version 4.02 (The R Foundation for Statistical Computing, Vienna, Austria). Specifically, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.

3. Results

3.1. Patient Characteristics

Between 15 February 2022 and 31 August 2022, 201 patients were admitted to our hospital. Among these patients, 13 were excluded due to duplicate cases admitted during the study period, and 32 were excluded owing to incomplete data on serum zinc or other factors. None were excluded for having a prior diagnosis of zinc deficiency or for taking zinc supplements. The study ultimately included 156 patients, with a mean age of 68.1 years (SD: 16.8). This cohort comprised 67 men and 89 women. While there were no significant differences in age or BMI between the genders, notable differences were observed in height and weight. The men were significantly taller (1.66 m [0.07] vs. 1.51 m [0.07]; $p < 0.001$) and heavier (66.5 kg [16.3] vs. 52.2 kg [12.3]; $p < 0.001$) than the women. Regarding hospital admission reasons, the incidence of fractures showed no significant difference ($p = 0.87$). However, spinal diseases were more prevalent in men than in women (31.3% vs. 15.7%; $p = 0.03$), and osteoarthritis (OA) was less frequent in men (9.0% vs. 25.8%; $p < 0.01$). The fracture details between the two groups revealed no significant disparities (Table 1).

Table 1. Baseline characteristics of study patients.

	Total (n = 156)	Men (n = 67)	Women (n = 89)	p value
Age, years	68.1 ± 16.8	65.2 ± 16.5	70.4 ± 16.9	0.06
Height, m	1.58 ± 0.10	1.66 ± 0.07	1.51 ± 0.07	<0.001 *
Weight, kg	58.4 ± 15.8	66.5 ± 16.3	52.2 ± 12.3	<0.001 *
BMI, kg/m ²	23.3 ± 5.1	24.0 ± 5.2	22.8 ± 5.0	0.12
Reason for hospitalization				
Fracture	69 (44.2%)	29 (43.3%)	40 (44.9%)	0.87
Spine	35 (22.4%)	21 (31.3%)	14 (15.7%)	0.03 *
Osteoarthritis	29 (18.6%)	6 (9.0%)	23 (25.8%)	<0.01 *
Others	23 (14.7%)	11 (16.4%)	12 (13.5%)	0.65
Details of fractures				
Fragility fracture	41 (26.3%)	15 (22.4%)	26 (29.2%)	0.36
Hip fracture	28 (17.9%)	15 (22.4%)	13 (14.6%)	0.29
Proximal humeral fracture	4 (2.6%)	0 (0%)	4 (4.5%)	0.14
Pelvic fracture	6 (3.8%)	3 (4.5%)	3 (3.4%)	1
Distal radius fracture	4 (2.6%)	1 (1.5%)	3 (3.4%)	0.64
Spine fracture	11 (7.1%)	5 (7.5%)	6 (6.7%)	1

* Statistically significant. BMI, body mass index.

3.2. Characteristics of cases (zinc deficiency) and Controls

We found that 47 (30.1%) patients had a zinc deficiency. The case and control groups were similar in terms of sex, height, and comorbidities, although there were significant differences in age, weight, and BMI. In particular, the mean (SD) age of the case group was significantly higher than that of the control group (75.5 years [13.8] vs. 65.0 years [17.1]; $p < 0.001$). The mean (SD) weight of the case group was significantly lower than that of the control group (53.8 kg [14.4] vs. 60.3 kg [16.1], respectively, $p = 0.02$). The mean (SD) BMI of the case group was significantly lower than that of the control group (21.7 kg/m² [4.5] vs. 24.0 kg/m² [5.2]; $p < 0.01$).

Regarding the reasons for hospitalisation, significant differences were observed between the case and control groups. The fracture rate was significantly higher in the case group than in the control group (68.1% vs. 33.9%; $p < 0.001$); spinal disease was significantly less common in the case group than in the control group (2.1% vs. 31.2%; $p < 0.001$); and OA was significantly less common in the case group than in the control group (8.5% vs. 22.9%; $p = 0.04$). The rates of fragility and hip and pelvic fractures were significantly higher in the case group than in the control group ($p < 0.001$, $p < 0.001$, $p < 0.01$, respectively). Among the medications, patients were significantly more likely to take iron supplements than controls (10.6% vs. 1.8%; $p = 0.03$) (Table 2).

Table 2. Characteristics of Zinc Deficiency and Controls.

Variables	Zinc deficiency (n = 47)	Control group (n = 109)	p value
Demographics			
Age, years	75.5 ± 13.8	65.0 ± 17.1	<0.001 *
Age category			
50 and above	45 (95.7%)	93 (85.3%)	0.1
60 and above	43 (91.5%)	76 (69.7%)	<0.01 *
70 and above	35 (74.5%)	52 (47.7%)	<0.01 *
80 and above	22 (46.8%)	17 (15.6%)	<0.01 *
90 and above	4 (8.5%)	2 (1.8%)	0.07
Women	25 (53.2%)	64 (58.7%)	0.6
Height, m	1.57 ± 0.10	1.58 ± 0.10	0.63
Weight, kg	53.8 ± 14.4	60.3 ± 16.1	0.02 *
BMI, kg/m ²	21.7 ± 4.5	24.0 ± 5.2	<0.01 *
High BMI **	8 (17.0%)	40 (36.7%)	0.01 *
Low BMI **	12 (25.5%)	15 (13.8%)	0.11
Normal BMI **	27 (57.4%)	54 (49.5%)	0.39
Associated comorbidity			
Diabetes mellitus	11 (23.4%)	24 (22.0%)	0.84
Hypothyroidism	4 (8.5%)	3 (2.8%)	0.2
GERD	5 (10.6%)	8 (7.3%)	0.53
Depression	1 (2.1%)	10 (9.2%)	0.18
Haemodialysis	2 (4.3%)	9 (8.3%)	0.51
Reason for hospitalization			
Fracture	32 (68.1%)	37 (33.9%)	<0.001 *
Spinal disease	1 (2.1%)	34 (31.2%)	<0.001 *
Osteoarthritis	4 (8.5%)	25 (22.9%)	0.04 *
Others	10 (21.3%)	13 (11.9%)	0.15
Details of fractures			
Fragility fracture	26 (55.3%)	15 (13.8%)	<0.001 *
Hip fracture	21 (44.7%)	7 (6.4%)	<0.001 *
Proximal humeral fracture	1 (2.1 %)	3 (2.8%)	1
Pelvic fracture	5 (10.6 %)	1 (0.9%)	<0.01 *
Distal radius fracture	0 (0 %)	4 (3.7%)	0.32
Spine fracture	3 (6.4 %)	8 (7.3%)	1
Medication use			
Zinc supplements	0 (0%)	0 (0%)	NA
Iron supplements	5 (10.6%)	2 (1.8%)	0.03 *
Magnesium supplements	10 (21.3%)	15 (13.8%)	0.24
Vitamin D supplements	4 (8.5%)	16 (14.7%)	0.43
Calcium supplements	3 (6.4%)	8 (7.3%)	1

Proton pump inhibitors	14 (29.8%)	26 (23.9%)	0.43
H2 receptor antagonists	0 (0%)	8 (17.0%)	0.11
Diuretics	8 (17.0%)	14 (29.8%)	0.62
Antihypertensive	31 (66.0%)	56 (51.4%)	0.11
Opioid	5 (10.6%)	14 (12.8%)	0.8
Antibiotics	2 (4.3%)	2 (1.8%)	0.58

* Statistically significant. ** Participants were classified into three groups based on BMI according to the classification of the Japan Society for the Study of Obesity: High BMI (BMI \geq 25), Normal (BMI 18.5 to 25), and Low BMI (BMI $<$ 18.5). BMI, body mass index; GERD, Gastroesophageal reflux disease.

3.3. Laboratory Findings

The case group exhibited a significantly lower mean serum zinc concentration, with a standard deviation (SD) of 46.2 μ g/dL (9.7), compared to the control group's mean (SD) of 76.3 μ g/dL (16.5) ($p < 0.05$). Moreover, patients with zinc deficiency had significantly lower mean blood concentrations of albumin (3.3 g/dL [0.7] vs. 4.0 g/dL [0.5]; $p < 0.001$) and haemoglobin (10.8 g/dL [2.0] vs. 13.1 g/dL [1.9]; $p < 0.001$) than did the control group. The incidence of hypoalbuminaemia was significantly higher in the case group than in the control group (74.5% vs. 23.9%, $p < 0.001$). Finally, the incidence of anaemia was significantly higher in the case group than in the control group (70.2% vs. 16.5%; $p < 0.001$) (Table 3).

Table 3. Laboratory Findings of patients with zinc deficiency and controls.

Variables	Zinc deficiency Control group value		
	(n = 47)	(n = 109)	
Zinc, μ g/dL	46.2 \pm 9.7	76.3 \pm 16.5	<0.001 *
Corrected calcium **	9.6 \pm 0.6	9.7 \pm 0.5	0.492
Hypocalcaemia ($<$ 8.8 mg/dL)	1 (2.1%)	1 (0.9%)	0.513
Albumin, g/dL	3.3 \pm 0.7	4.0 \pm 0.5	<0.001 *
Hypoalbuminemia ($<$ 3.8 g/dL)	35 (74.5%)	26 (23.9%)	<0.001 *
Creatine, mg/dL	1.5 \pm 1.8	1.4 \pm 2.2	0.79
eGFR, mL/min/1.73 m ²	60.8 \pm 34.0	66.6 \pm 28.3	0.28
Haemoglobin, g/dL	10.8 \pm 2.0	13.1 \pm 1.9	<0.001 *
Anaemia (Hb $<$ 11.0 g/dL in Women, Hb $<$ 13.0 g/dL in Men)	33 (70.2%)	18 (16.5%)	<0.001 *
Haemoglobin A _{1c} , %	6.0 \pm 1.0	5.9 \pm 0.7	0.38
ALP (IFCC), U/L	89.9 \pm 31.2	89.8 \pm 38.7	0.99

* Statistically significant. ** The corrected calcium concentration was determined using the following formula. Corrected Ca concentration = measured Ca concentration + (4 - albumin concentration). eGFR, estimated glomerular filtration rate; ALP (IFCC), Alkaline Phosphatase; (International Federation of Clinical Chemistry and Laboratory Medicine).

3.4. Predictors of zinc deficiency

According to univariate analysis, statistically significant indicators ($p < 0.05$) were included in multivariate logistic regression analysis, including age ($p < 0.001$), age \geq 60 ($p < 0.01$), age \geq 70 ($p < 0.01$), age \geq 80 ($p < 0.01$), weight ($p = 0.02$), BMI ($p < 0.01$), high BMI ($p = 0.01$), fracture ($p < 0.001$), spinal disease ($p < 0.001$), OA ($p = 0.04$), fragility fracture ($p < 0.001$), hip fracture ($p < 0.001$), pelvic fracture ($p < 0.01$), and iron supplements ($p = 0.03$). The following indicators, which were not significant but had $p < 0.15$, were also included in multivariate logistic regression analysis, including age \geq 50 ($p = 0.10$), age \geq 90 ($p = 0.07$), low BMI ($p = 0.11$), H2 receptor antagonists ($p = 0.11$), and antihypertensive ($p = 0.11$). The multiple logistic regression analysis identified that age \geq 60 (odds ratio [OR], 15.40; 95% confidence interval [CI], 1.30–182.00; $p = 0.03$), anaemia (OR, 9.80; 95% CI, 3.16–30.40; $p < 0.001$), hip fracture (OR, 5.67; 95% CI, 1.64–19.60; $p < 0.01$), and hypoalbuminaemia (OR, 4.76; 95% CI, 1.49–15.20; $p < 0.01$) were independent predictive factors of zinc deficiency. The results

also indicated that spinal disease was associated with a lower risk of zinc deficiency (OR, 0.04; 95% CI, 0.004–0.45; $p < 0.01$) (Table 4).

Table 4. Predictive factors associated with Zn deficiency.

	OR	95% CI	<i>p</i> value
(Intercept)	0.34	0.02–5.83	0.46
Age ≥ 60	15.40	1.30–182.00	0.03 *
Anaemia (Hb < 11.0 g/dL in Women, Hb < 13.0 g/dL in Men)	9.80	3.16–30.40	<0.001 *
Hip fracture	5.67	1.64–19.60	<0.01 *
Hypoalbuminemia (<3.8 g/dL)	4.76	1.49–15.20	<0.01 *
Spinal disease	0.04	0.004–0.45	<0.01 *
Pelvic fracture	10.40	0.60–180.00	0.11
Age ≥ 80	4.10	0.92–18.20	0.06
Age (years)	0.94	0.88–1.01	0.08

* Statistically significant. OR, odds ratio.

4. Discussion

This study found that 30.1% of inpatients in the orthopaedic department had zinc deficiency based on serum zinc concentrations. Furthermore, our study demonstrated that age ≥ 60 , anaemia, hip fracture, and hypoalbuminaemia were independent predictive factors of zinc deficiency. Additionally, our study identified a correlation between spinal disease and a decreased likelihood of zinc deficiency. Concerning zinc deficiency prevalence, Yokokawa et al. conducted research involving 2056 Japanese adults (mean age 63.8 years [standard deviation 14.0]) participating in a voluntary health checkup at a single hospital [26]. Their study found that zinc deficiency, defined as serum zinc levels below 60 $\mu\text{g/dL}$, was present in 0.4% of males and 0.6% of females. In contrast, our study observed a zinc deficiency prevalence of 30.1%, markedly diverging from Yokokawa et al.'s results. This disparity suggests that zinc deficiency is a pathophysiological condition frequently encountered in orthopaedic practice.

Gau et al. conducted a retrospective prevalence study involving 157 community residents aged 50 years or older, regularly followed up at a geriatric clinic in southeast Ohio [27]. They concluded that a previous hip fracture was a significant risk factor for zinc deficiency (OR, 9.65; 95% CI, 1.64–19.60; $p < 0.01$). In our hospital-based study, we also identified hip fracture as a predictive factor for zinc deficiency (OR, 5.67; 95% CI, 1.64–19.60; $p < 0.01$), consistent with the findings of Gau et al. We speculate that hip fractures serve as a predictor of zinc deficiency because of the involvement of background factors such as osteoporosis, a well-established contributor to zinc deficiency [28]. A study involving 122 osteoporotic patients aged 65 years and over with zinc deficiency demonstrated a significant increase in bone mineral density from baseline after 6 and 12 months of zinc treatment [29]. Consequently, in cases where osteoporosis is present in patients with hip fractures, monitoring zinc levels is advisable, and zinc supplementation should be considered if a deficiency is detected.

The association between zinc and anaemia has been extensively documented in women of reproductive age [30–33], preschool-aged children [34–36], and adults [37,38]. Consistent with these findings, our multivariate logistic regression analysis revealed that anaemia was a significant predictor of zinc deficiency (OR, 9.80; 95% CI, 3.16–30.40; $p < 0.001$). It is hypothesized that the mechanism underlying anaemia related to zinc deficiency involves impaired functionality of the zinc finger protein GATA-1, crucial for the differentiation and proliferation of erythroblasts [39]. Jeng and Chen conducted a literature review, concluding that zinc status warrants careful monitoring and that zinc supplementation could potentially prevent and treat anaemia [40]. Should anaemia remain refractory to treatment, the possibility of zinc deficiency ought to be considered.

In this study, patients with zinc deficiency exhibited a significantly higher rate of hypoalbuminemia (serum albumin < 3.8 g/dL) than did controls (74.5% vs. 23.9%; $p < 0.001$). Notably, hypoalbuminemia is one of the predictive factors for zinc deficiency (OR, 4.76; 95% CI, 1.49–15.20; p

<0.01). These findings are consistent with those of previous studies [23,27]. Serum zinc concentrations may be influenced by the status of zinc-binding proteins, such as albumin, which binds approximately 80–85% of serum zinc [41]. Conversely, zinc deficiency may affect albumin synthesis. A prior study demonstrated that serum albumin concentrations improved following zinc supplementation in individuals with severe zinc deficiency [42]. Therefore, if either zinc deficiency or hypoalbuminemia is identified, investigating the other is advisable.

This study had several limitations. Firstly, it was a retrospective study with a relatively small sample size, and the data were confined to a single centre. Secondly, the study exclusively included Japanese individuals, and race or ethnicity was not considered as a variable in the logistic regression analysis. Thirdly, background factors like osteoporosis were not assessed in multiple logistic regression analyses. To overcome these limitations, it is imperative to conduct large-scale, multinational clinical trials. This study is anticipated to act as a stimulus for such initiatives.

5. Conclusions

This study identified zinc deficiency in 30.1% of orthopaedic inpatients based on serum zinc concentrations. Furthermore, age ≥ 60 , anaemia, hip fracture, and hypoalbuminaemia were determined as independent predictive factors for zinc deficiency.

Author Contributions: Conceptualization, T.S.; methodology, T.S.; software, T.S.; validation, T.S., D.I. and Y.Y.; formal analysis, T.S.; investigation, T.S.; resources, T.S.; data curation, D.I.; writing—original draft preparation, T.S.; writing—review and editing, T.S.; visualization, Y.Y.; supervision, Y.M.; project administration, Y.M. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Because this was a retrospective study, the requirement for informed consent was waived.

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Conflicts of Interest: The authors declare no conflict of interest.

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