[**Original Research**]

Significance of Serum Essential Trace Element Measurements in Terminal Cancer Patients—Correlations between Serum Iron, Copper, Zinc and Cachexia-Related Proteins—

Akihiro ITO,[*1] Masanobu USUI,[*1] Norimasa TSUZUKI,[*1]
Akihiko FUTAMURA,[*1] Miyo MURAI,[*1] Hiroyuki FUJISAKI,[*1]
Kazuki IMAI,[*1] Yoshinori ITANI,[*2] and Miwa ARAKI[*3]

[*1] Department of Surgery and Palliative Medicine, Fujita Health University School of Medicine
[*2] Department of Medical Technology, Clinical Examination Division, Fujita Health University Nanakuri Memorial Hospital
[*3] Department of Pharmacy, Fujita Health University Nanakuri Memorial Hospital

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Abstract:

Background & Aims: Essential trace elements (ETEs) cannot be synthesized in vivo and must be ingested. Terminal cancer patients face concerns about the risk of trace element deficiency due to malnutrition. However, no studies appear to have comprehensively examined nutritional indicators or serum concentrations of trace elements among terminal cancer patients. We investigated correlations between the dynamics of serum ETEs and proteins related to cachexia.

Methods: This study investigated 176 terminal cancer patients hospitalized between April 2018 and March 2019, after excluding patients already diagnosed with refractory cachexia at the time of admission and those who died within 10 days of admission. Cachexia-related proteins and serum trace elements were measured and correlations were examined.

Results: Serum transthyretin (TTR) and albumin (Alb) values on admission were below standard values in all cases, and C-reactive protein (CRP) values were above the reference range in 81.9% of patients. No correlations were found between serum iron levels and serum TTR, Alb, and CRP levels. Significant correlations existed between serum zinc levels and serum TTR, Alb, and CRP levels. No correlations were found between serum copper levels and serum TTR, Alb, and CRP levels. Correlations between serum zinc levels and serum TTR and CRP levels were stronger in the 68 patients who received nutritional management for 1 month compared to correlations on admission.

Conclusions: Patients with terminal cancer often show abnormalities in ETEs. Serum zinc levels correlated with cachexia-related proteins, suggesting that zinc may affect prognostic factors.

Key words: essential trace element, cachexia, terminal cancer, zinc, cachexia-related protein

INTRODUCTION

Like vitamins, essential trace elements (ETEs) such as zinc, iron, copper, manganese, iodine, cobalt, chromium, selenium and molybdenum are present in living tissues in very small amounts. Moreover, ETEs cannot be synthesized in vivo, but are contained in the body as core components of enzymatic activity, and are essential in protein metabolism and other biological processes.[1, 2] Terminal cancer patients are typically deficient in ETEs due to a number of factors, including: 1) inadequate oral intake; 2) impaired absorption due to decreased gastrointestinal (GI) function or malabsorption syndrome; 3) increased excretion or depletion due to loss via the GI tract, GI bleeding or excretion into urine; and 4) other reasons such as interactions with other trace elements. Zinc deficiency can lead to taste disorder, pressure ulcers, stomatitis and refractory dermatitis, while copper and iron deficiencies can cause anemia. These deficiencies exacerbate the suffering of terminal cancer patients and must therefore be corrected. Long-term, high-calorie total parenteral nutrition (TPN) not supplemented with trace elements has been reported to cause zinc and copper deficiencies,[3] underlining their importance in clinical settings.

In addition to the illness and impairment in terminal cancer patients, these individuals are often elderly. The effects of aging on patients with terminal cancers include not only reduced dietary intake, but also decreased physical and mental activity, which may in turn cause progression of cachexia and protein energy malnutrition.

Corresponding author: Akihiro Ito, Department of Surgery and Palliative Medicine, Fujita Health University School of Medicine, 424-1 Otori-cho, Tsu, Mie 514-1295, Japan
E-mail: itoh@mctv.ne.jp

In patients with chronic debilitating disease presenting with cachexia, persistent chronic hypercytokinemia can cause anorexia, chronic inflammation and increased proteolysis, among other ailments. In cancers, cachexia putatively involves factors such as unique metabolic reactions in the tumor and proteolysis-inducing factor (PIF)[4] and lipid-mobilizing factor (LMF)[5] released from the tumor. PIF causes degradation of skeletal muscle and loss of lean body mass via the ubiquitin-proteasome pathway, whereas LMF creates a negative metabolic balance by promoting the hydrolysis of triglycerides and increasing oxygen consumption in adipose tissue. The complex interaction of these factors can trigger the onset of cancer cachexia, characterized by reductions in body fat and skeletal muscle.

Although the use of replacement therapies to treat the depletion of ETEs due to invasion has been reported in elderly patients,[6] no studies appear to have comprehensively investigated indices of nutrition and cachexia or serum concentrations of ETEs in terminal cancer patients. We sought to address this gap in the knowledge by investigating correlations between serum ETE kinetics and cachexia-related proteins.

MATERIALS AND METHODS

Participants

Study participants were selected from among all 245 terminal cancer patients who were admitted to Fujita Health University's Nanakuri Memorial Hospital for palliative care within the 12-month period from April 2018 to March 2019. A total of 176 patients were enrolled in the study, after excluding 36 patients already diagnosed with refractory cachexia prior to admission and 33 patients who died within 10 days of admission. We defined terminal cancer patients as patients who would not achieve cure from the cancer by treatments based on objective data (imaging diagnosis, general hematology, etc.) obtained from multiple doctors and with an estimated prognosis of within 3 months.

Refractory cachexia can be classified according to the three disease stages proposed by Fearon et al.,[7] and has been defined as pronounced irreversible malnutrition due to advanced cancer progression, or as genuinely terminal clinical features such as pleural effusion, ascites or generalized edema that cannot be controlled with diuretics, puncture drainage or cell-free and concentrated ascites reinfusion therapy.[8]

The study was approved by the Medical Research Ethics Review Board at Fujita Health University (approval no. HM16-401).

Measurement of serum TTR, Alb and CRP

Clinical assessments comprised general hematology, specifically cachexia-related indices in the form of serum transthyretin (TTR), albumin (Alb), C-reactive protein (CRP) and serum ETE levels (iron [Fe], copper [Cu] and zinc [Zn]). Blood samples were collected before breakfast in the fasted state, with the same serum sample used for analysis. After collection, blood was mixed by inversion approximately 10 times, and collected in an upright blood collection tube so that the blood did not come into contact with the rubber stopper. After coagulation, centrifugation was performed at 3000 rpm for 10 min, and the analysis was performed immediately thereafter. If analyses could not be performed immediately after centrifugation, the sample was stored in a refrigerator at 4℃. Blood samples were analyzed using an AU680 automatic analyzer (Beckman Coulter, Osaka, Japan).

TTR was measured by the turbidimetric immunoassay method using Espa/TTRII reagent (Nipro Co., Osaka, Japan), Alb was measured by the improved bromocresol purple method using AU reagent ALB (Beckman Coulter), and CRP was measured by the latex aggregation method using AU reagent CRP (Beckman Coulter). Reference ranges for serum TTR, Alb and CRP levels were 22–44 mg/dL, 4.0–5.0 g/dL and $\leq$ 0.7 mg/dL, respectively.

Measurement of serum iron, zinc and copper

Iron was assayed by a colorimetric method using a quick auto neo Fe (Shino-Test Corporation, Sagamihara, Japan). Iron in the sample is bound to transferrin in globulin. Fe^{3+} bound to this transferrin is released under acidic conditions and is reduced to Fe^{2+} with a reducing agent (ascorbic acid). Fe^{2+} forms a chelate compound with nitroso-PSAP (2-(5-nitro-2-pyridylazo)-5-[N-n-propyl-N-(3-sulfopropyl) amino] phenol, disodium salt, dihydrate), resulting in coloration and allowing colorimetric determination of the serum iron level. Copper was likewise assayed using a colorimetric method with Espa·Cu reagent (Nipro Co.). Copper forms a chelate compound with 3,5-DiBr-PAESA (4-(3,5-dibromo-2-pyridylazo)-N-ethyl-N-(3-sulfopropyl) aniline, monosodium salt, monohydrate), causing a change in color. The concentration of copper in serum is calculated from the amount of change in absorbance. Zinc was assayed by colorimetric method using Espa·ZnII reagent (Nipro Co.). Zn^{2+} forms a chelate compound with nitroso-PSAP and develops color. Serum zinc level is then measured by colorimetry. Reference ranges for serum iron levels were 65–200 μg/dL for men and 50–160 μg/dL for women, while reference ranges for serum copper and zinc levels were 68–128 μg/dL and 65–135 μg/dL, respectively.

Administration of drugs related to study result

We investigated the administration of drugs that may have affected the study results. On admission, sodium ferrous citrate was being administered to 13 patients (7.4%) with mean serum iron concentrations of 35.1 $\pm$ 30.0 μg/dL (median, 27 μg/dL), and polaprezinc was being administered in 3 patients (1.7%) with serum zinc concentrations of 58, 57, and 80 μg/dL, respectively. No cases of high serum iron and zinc concentrations were observed in the patients administered these drugs. Moreover, no patients were being administered anamorelin hydrochloride, a drug sometimes used to treat cachexia. In the patients administered sodium ferrous citrate and polaprezinc, which were considered likely to affect the study results, none showed high serum iron and zinc levels, but no health food surveys could be conducted. Patients administered drugs were therefore not excluded.

Study design

Study 1: Correlations between serum cachexia-related proteins and ETEs in all cancer patients

Cachexia-related proteins and serum trace elements were measured and correlations were examined in 176 terminal cancer patients at admission.

Study 2: Correlations between serum cachexia-related proteins and ETEs, especially comparison of parameters on admission between patients < 65 and ≥ 65 years old

Since many terminal cancer patients are elderly and may be affected by aging, we divided them into 21 patients under 65 years old and 155 patients over 65 years old, and conducted the same investigations.

Study 3: Correlations between serum cachexia-related proteins and ETEs, especially comparison of parameters on admission and 1 month after admission

Assays were repeated for the 68 patients from whom blood samples were also obtained after approximately 1 month (28–35 days after admission) of nutritional management. In cases where malnutrition is diagnosed from nutritional evaluations and energy requirements are considered unable to be reached by oral intake alone, intravenous nutrition is basically performed. Of the 108 patients from whom blood could not be collected 1 month after admission, 93 had died within that 1 month, 13 were near death at 1 month after admission, and 2 patients declined further blood collection. In addition, we investigated the administration of drugs that may have affected this study. Seven patients (10.3%) continued to be administered sodium ferrous citrate after admission. Of these, 3 patients were administered 100 mg/day for 1 month, two were administered 50 mg/day for 1 month, one was administered 100 mg/day for 15 days, and one was administered 50 mg/day for 4 days. One patient (1.5%) continued to be administered polaprezinc after admission, at 150 mg/day for 1 month. Moreover, parenteral nutrition was performed for 54 of the 68 cases (79.4%). Iron was intravenously administered at 2.67 ± 0.06 μmol/day, copper at 0.72 ± 0.02 μmol/day, and zinc at 13.8 ± 0.3 μmol/day. Since the amount of ETEs taken orally cannot be calculated in practice, cases of drug administration including parenteral infusion were not excluded.

Statistical analysis

Assay results are expressed as mean ± standard deviation. Statistical testing for correlations was performed using Pearson's correlation coefficient, with values of $p < 0.05$ considered to indicate a significant difference and r values of ≥ 0.4 or ≤ −0.4 indicating a correlation. Continuous variables were calculated using the unpaired t-test. Differences were considered significant for values of $p < 0.05$.

RESULTS

[Study 1]

Median age was 73 years and participants comprised 97 men and 79 women. Primary tumor sites by incidence were the lungs in 41 patients (23.2%), pancreas in 23 patients (13.0%), stomach in 22 patients (12.4%), colon in 20 patients (11.3%), renal/urinary system in 13 patients (7.3%), uterus/ovary in 12 patients (6.8%) and hepatobiliary system in 9 patients (5.1%). Patient prognosis from the date of admission was 34.6 ± 20.4 days (Table 1). Serum TTR and Alb levels on admission (i.e., baseline) were below the reference range and indicative of malnutrition in all patients, with mean values of 10.5 ± 5.7 mg/dL and 2.6 ± 0.7 g/dL, respectively. In contrast, the mean CRP level was 6.8 ± 6.9 mg/dL, which exceeded the reference range in 145 of the 176 patients (81.9%).

The mean iron level was 21.5 ± 29.0 μg/dL, which were below the reference range in 155 of the 176 patients (88.1%). The mean zinc level was 54.8 ± 15.4μg/dL, which were below the reference range in 127 of the 176 patients (72.2%). The mean copper level was 108.8 ± 37.0 μg/dL, which were below the reference range in 14 of the 176 patients (8.0%). (Table 2).

Correlations between respective serum levels of cachexia-related proteins TTR, Alb, and CRP and serum levels of ETE iron, zinc and copper are shown in Fig. 1. No correlations were evident between serum iron and serum TTR, Alb and CRP levels, despite the presence of significant differences (TTR: $r = 0.2825$, $p = 0.0003$; Alb: $r = 0.3644$, $p < 0.0001$; CRP: $r = -0.3454$, $p < 0.0001$). However, significant mild correlations were apparent between serum zinc and each of serum TTR, Alb and CRP levels (TTR: $r = 0.4531$, $p < 0.0001$; Alb: $r = 0.4882$, $p < 0.0001$; CRP: $r = -0.4168$, $p < 0.0001$). No significant differences or correlations were evident between serum copper and serum TTR or Alb levels (TTR: $r = -0.1255$, $p = 0.0990$; Alb: $r = 0.1393$, $p = 0.0668$), and this lack of correlation also applied to CRP levels despite the presence of significant differences

Table 1 Characteristics of patients

Factor	$n = 176$
Age (years, median)	73 (33–96)
Sex (male / female)	97 / 79
Cancer type (cases)	
Lung	41
Pancreas	23
Stomach	22
Colon	20
Urology	13
Gynecology	12
Hepatobiliary	9
Breast	7
Pharyngeal	4
Malignant lymphoma	4
Other	21
Hospital stay (days)	34.6 ± 20.4 (10–100)

Table 2 Laboratory data

	Study 1	Study 2			Study 3		
Blood sampling	Admission	Admission			Admission	1 month after admission	
Factor	All	< 65 years old	≥ 65 years old	*p* value	1-month nutritional management		*p* value
n	176	21	155		68	68	
TTR (mg/dL)	10.5 ± 5.7	9.9 ± 6.7	10.6 ± 5.6	0.5642	12.1 ± 5.2	9.7 ± 4.6	0.0045
Alb (mg/dL)	2.6 ± 0.7	2.3 ± 0.6	2.7 ± 0.7	0.0297	2.8 ± 0.7	2.4 ± 0.6	0.0006
CRP (mg/dL)	6.8 ± 6.9	9.9 ± 8.1	6.4 ± 6.8	0.0349	5.2 ± 6.2	8.5 ± 8.1	0.0087
Fe (μg/dL)	36.3 ± 29.7	30.3 ± 21.1	37.3 ± 37.2	0.3320	39.9 ± 37.2	33.6 ± 22.4	0.2650
Zn (μg/dL)	54.8 ± 15.4	51.4 ± 15.6	55.1 ± 15.3	0.3113	56.8 ± 13.5	57.1 ± 17.0	0.7206
Cu (μg/dL)	108.8 ± 37.0	123.4 ± 55.9	118.8 ± 34.1	0.5966	118.7 ± 35.5	118.5 ± 31.8	0.9840

Table 3 Correlations between serum levels of iron, zinc, copper and cachexia related proteins in all cancer patients on admission ($n = 176$)

	Fe		Zn		Cu	
	r	*p* value	*r*	*p* value	*r*	*p* value
TTR	0.2825	0.0003	0.4531	< 0.0001	− 0.1255	0.0990
Alb	0.3644	< 0.0001	0.4882	< 0.0001	0.1393	0.0668
CRP	− 0.3454	< 0.0001	− 0.4168	< 0.0001	0.3178	< 0.0001

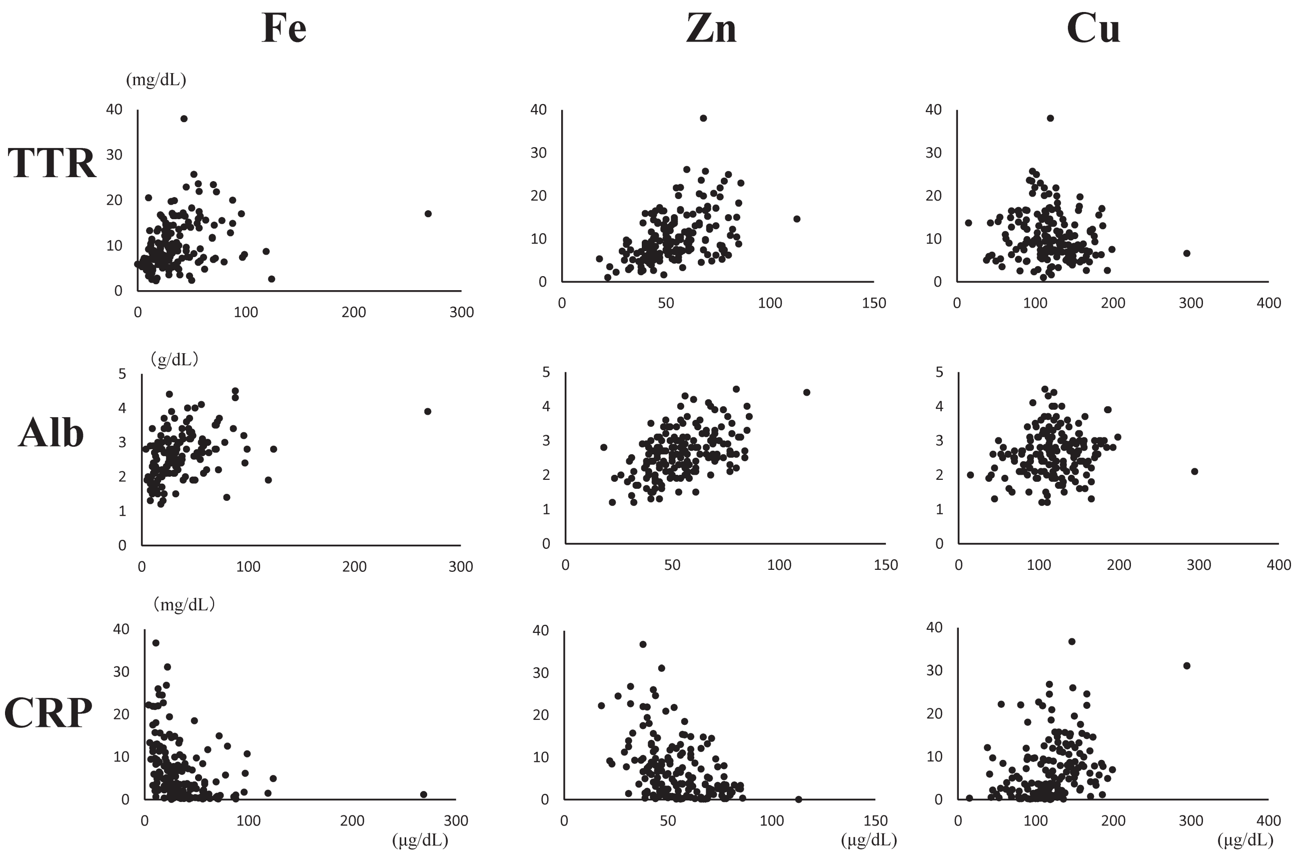

Fig. 1 Correlations between serum levels of iron, zinc, copper and cachexia-related proteins ($n = 176$).

(CRP: $r = 0.3178$, $p < 0.0001$) (Table 3, Fig. 1). Copper is a known antagonist of zinc absorption in the GI tract. The correlation between serum copper and zinc levels was therefore examined, but no negative correlation was found ($r = 0.0355$, $p = 0.6418$, Fig. 2).

[Study 2]

Next, patients were divided into 21 patients under 65 years old and 155 patients over 65 years old. As a background factor, prognosis was 23.5 ± 10.1 days in patients under 65 years old, but significantly shorter in patients over 65 years old (36.1 ± 20.8 days; $p = 0.0009$). Serum TTR, Alb, CRP and serum ETEs (iron, copper, zinc) were then compared between groups as cachexia-related indicators. Serum Alb level was significantly lower and CRP level was significantly higher in patients under 65 years old than in patients over 65 years old. Serum iron, copper and zinc levels did not differ significantly between these two groups (Table 2). In patients under 65 years old, serum iron levels and serum TTR, Alb, and CRP levels correlated significantly (TTR: $r = 0.4716$, $p = 0.0309$; Alb: $r = 0.4901$, $p = 0.0241$; CRP: $r = -0.5740$, $p = 0.0065$). Serum zinc levels and serum TTR and Alb levels were significantly correlated in both groups, with patients under 65 years old showing stronger correlations than patients over 65 years old. In patients over 65 years old, serum zinc levels and serum CRP levels were significantly correlated (CRP: $r = -0.4355$, $p < 0.0001$). In patients under 65 years old, serum copper levels and serum CRP levels were significantly correlated (CRP: $r = 0.6758$, $p = 0.0008$) (Table 4, Fig. 3).

[Study 3]

Serum TTR and Alb levels after 1 month of nutritional management in the 68 patients with cachexia were consistently lower than the respective baseline levels on admission, at 9.7 ± 4.6 mg/dL and 2.4 ± 0.6 g/dL versus 12.1 ± 5.2 mg/dL and 2.8 ± 0.7 g/dL, with all patients exhibiting malnutrition. On the other hand, CRP levels after nutritional management were elevated from the baseline of 5.2 ± 6.2 mg/dL to 8.5 ± 8.1 mg/dL, increasing beyond the reference range in 66 patients (97.1%) (Table 2). Significant mild correlations were seen between serum iron and serum TTR and CRP levels after nutrition management (TTR: $r = 0.445$, $p < 0.0001$; Alb: $r = 0.317$, $p < 0.0126$; CRP: $r = -0.4177$, $p = 0.0005$). Serum zinc levels after nutritional management correlated more strongly with serum TTR and CRP levels than on admission (TTR: $r = 0.673$, $p < 0.0001$; Alb: $r = 0.504$, $p < 0.0001$; CRP: $r = -0.417$, $p = 0.0005$). No significant differences or correlations were seen between serum copper and serum TTR and Alb levels after nutrition management, and this lack of correlation again applied to CRP levels despite the presence of significant differences (CRP: $r = 0.2667$, $p < 0.0331$) (Table 5, Fig. 4).

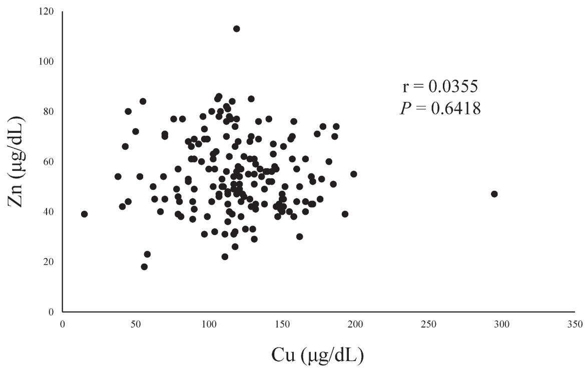

Fig. 2 Correlation between Cu and Zn levels.

DISCUSSION

Cachexia in patients with recurrent or advanced cancers is characterized by significant deletion of both adipose tissue and skeletal muscle.[9, 10] Pathophysiologically, cachexia is characterized by a negative protein-energy balance due to decreased oral intake and metabolic abnormalities.[11] Murai et al. identified interleukin-8 and clinical symptoms as indicators of prognosis in advanced cancer patients with cachexia, with patients in the poor-prognosis cohort exhibiting significantly lower serum Alb and TTR levels and significantly higher CRP levels than their counterparts in the favorable-prognosis cohort.[12] Miura et al. also reported that the Glasgow Prognostic Score,[13] defined by serum Alb and CRP levels, offers an important prognostic factor among cancer patients in palliative care settings.[14] In a separate study, Miura et al. reported serum TTR level as another important prognostic factor reflecting nutrition in palliative care settings.[15]

On the other hand, ETEs such as iron, copper and zinc are expected to decrease in terminal cancer patients with poor oral intake. However, no reports in the literature appear to provide detailed measurements of serum iron, copper and zinc levels in terminal cancer patients with malnutrition due to poor dietary intake of these elements. A previous study examining the relationship between trace elements and nutrition reported that zinc ingested from food is mainly absorbed via the duodenum and jejunum, with about two-thirds of zinc in the blood loosely bound to Alb and the remaining one-

Table 4 Correlations between serum levels of iron, zinc, copper and cachexia related proteins: comparison of parameters on admission between patients < 65 and ≥ 65 years old

		Fe		Zn		Cu	
	Age	r	p value	r	p value	r	p value
TTR	< 65 (n = 21)	0.4716	0.0309	0.5651	0.0076	− 0.2947	0.1947
	≥ 65 (n = 155)	0.2655	0.0018	0.4336	< 0.0001	− 0.0809	0.3205
Alb	< 65 (n = 21)	0.4901	0.0241	0.6102	0.0033	− 0.1368	0.5544
	≥ 65 (n = 155)	0.3504	< 0.0001	0.4716	< 0.0001	0.2094	0.0094
CRP	< 65 (n = 21)	− 0.5740	0.0065	− 0.3507	0.1191	0.6758	0.0008
	≥ 65 (n = 155)	− 0.3150	0.0002	− 0.4355	< 0.0001	0.2282	0.0046

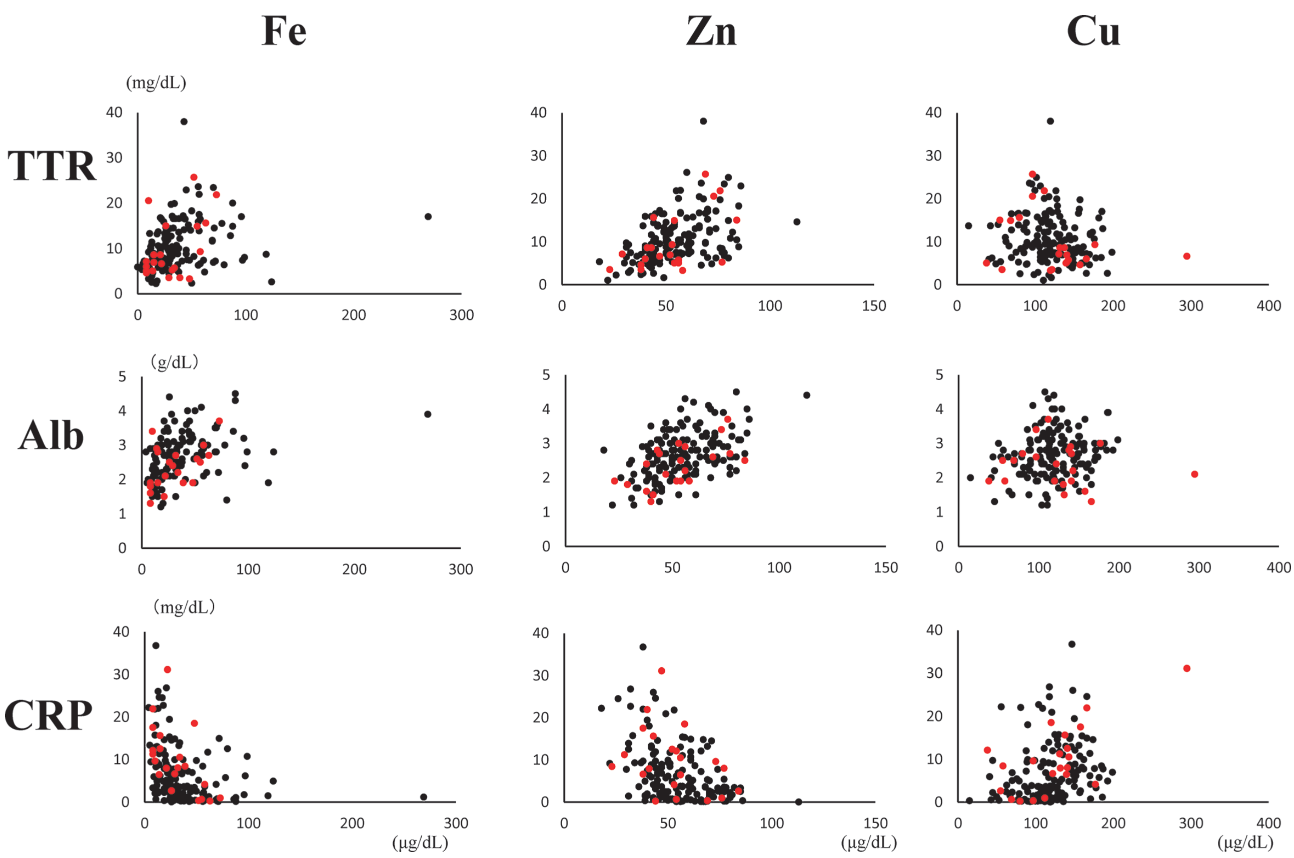

Fig. 3 Correlations between serum levels of iron, zinc, copper and cachexia-related proteins. ●: ≥ 65 years old (n = 155), ●: < 65 years old (n = 21).

Table 5 Correlations between serum levels of iron, zinc, copper and cachexia related proteins: data on admission and 1 month after admission in 68 patients who underwent 1 month nutritional management

		Fe		Zn		Cu	
		r	p value	r	p value	r	p value
TTR	Admission	0.3266	0.0102	0.4165	0.0004	− 0.1376	0.2706
	1 month after admission	0.4447	0.0003	0.6731	< 0.0001	− 0.1461	0.2494
Alb	Admission	0.3958	0.0016	0.5146	< 0.0001	0.1664	0.1817
	1 month after admission	0.3176	0.0126	0.5042	< 0.0001	− 0.1943	0.1239
CRP	Admission	− 0.3159	0.0131	− 0.2869	0.0177	0.3922	0.0011
	1 month after admission	− 0.4177	0.0005	− 0.4172	0.0005	0.2667	0.0331

third tightly bound to α-2 macroglobulin.[16] Accordingly, Goda et al. reported that a high proportion of healthy elderly individuals who are also hypoalbumic have serum zinc concentrations below the reference range, and that serum Alb and zinc levels are strongly correlated.[6] However, no reports in the literature appear to have investigated the relationship between ETE and nutritional indices in terminal cancer patients. The present study investigated potential correlations between ETEs and TTR, and Alb and CRP levels as indices of nutrition and cachexia based on the hypothesis that iron, zinc and other ETEs are somehow related to nutritional status.

Our findings showed that the terminal cancer patients were malnourished, with all participants exhibiting serum TTR and Alb levels below the respective reference ranges. In contrast, CRP levels exceeded the reference range in more than 80% of participants. Serum levels of the ETEs iron and zinc were below the respective reference ranges in many study participants. Blood tests on admission showed a significant correlation between serum zinc and serum TTR, Alb and CRP levels. Even stronger correlations were apparent between serum iron and zinc levels and serum TTR, Alb and CRP levels among those participants who received 1 month of

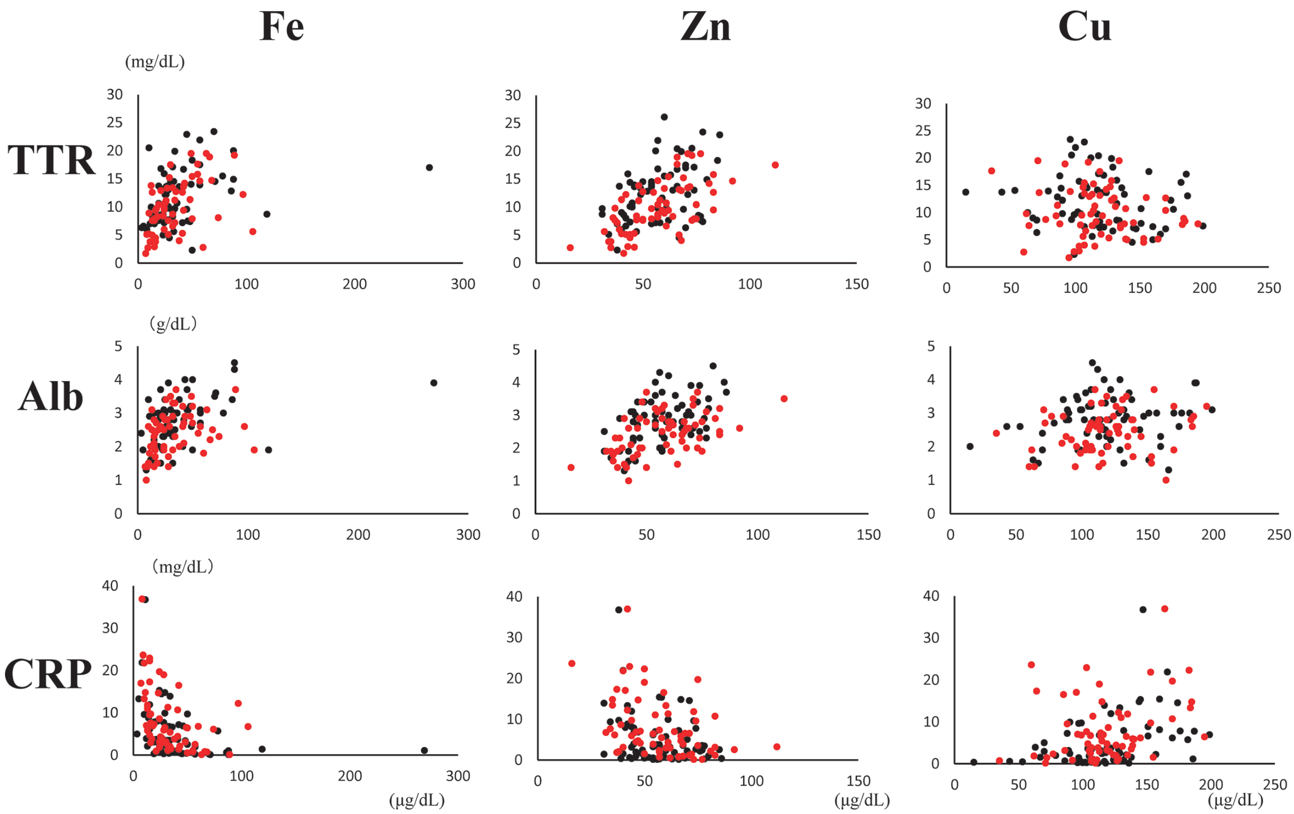

Fig. 4 Correlations between serum levels of iron, zinc, copper and cachexia-related proteins: data on admission and 1 month after admission who underwent 1-month nutritional management. ● : on admission (*n* = 68), ● : 1 month after admission (*n* = 68).

nutritional management. This finding suggests that the ETEs iron and zinc are closely related to nutritional status in patients with cachexia, and may influence the putative prognostic factors of TTR, Alb and CRP.

In our study, classifying cases into patients under 65 years old and over 65 years old, serum Alb level was significantly lower and CRP level was significantly higher in patients under 65 years old than in those over 65 years old. Furthermore, prognosis was significantly shorter in patients under 65 years old than in those over 65 years old. We presumed that many patients under 65 years old have a short prognosis from hospitalization and are hospitalized after their condition worsens. Serum Alb, TTR, iron, and zinc levels were strongly correlated in patients under 65 years old. A strong correlation was identified between CRP and both iron and copper levels in patients under 65 years old, and a strong correlation was found between CRP and zinc levels in patients over 65 years old. In other words, the reason why patients under 65 years old had a stronger correlation between ETEs and cachexia-related proteins than patients over 65 years old might be the difference in GI digestion and absorption of ETEs with age. However, the details remain unclear and this issue should be investigated more closely in the future.

In patients who underwent 1 month of nutritional management including intravenous administration of ETEs, serum iron and zinc levels correlated even more strongly with TTR and CRP levels. Although these findings could be partially attributable to the progression of cancer cachexia, many other possible factors are present in terminal cancer patients, such as dehydration (hematological evidence of apparent elevated TTR and Alb levels), GI absorption disorders and bleeding (hematological evidence of iron deficiency). Many patients are dehydrated at the time of admission, and hematological data often show high serum TTR and Alb levels. After admission, dehydration may be corrected by intravenous nutrition, serum TTR and Alb levels may decrease, and hematological data may reflect the original cachexia. Furthermore, terminal cancer patients may have digestive and absorptive disorders, and many patients in this study did not show normalization of serum iron and zinc levels despite treatment with sodium ferrous citrate and polaprezinc. That is, in cancer cachexia patients with malnourishment, serum ETEs are often below desirable levels. As a result of intravenous nutrition containing ETEs in such cases, serum iron and zinc levels 1 month after admission had not decreased further and were maintained. After 1 month of nutritional management following admission, serum TTR level was decreased and CRP level was increased due to the effects of cachexic deterioration. That is, as a result of appropriate administration of intravenous nutrition containing ETEs in addition to symptomatic palliative medicine such as blood transfusion and relief for total pain, TTR, CRP, iron and zinc levels were found to be more strongly correlated in patients with terminal cancer. However, the details remain unclear and further research is warranted.

In particular, zinc is involved in a wide range of physiological functions, particularly maintaining immune function, transferring genetic information, promoting wound healing, exerting antioxidant properties, maintaining neurotransmission and regulating bone metabolism. Moreover, zinc deficiency is associated with a range of ailments, including taste disorder, pressure ulcers, anorexia, diet refusal, glossodynia, stomatitis, decreased vitality, depression, intractable dermatitis, alopecia, anemia, diarrhea, reduced immune function and delayed wound healing.[17] None of the study participants developed any serious symptoms as a result of zinc deficiency, which may have been partly due to the administration of replacement therapy in the form of parenteral nutrition. Adequate care needs to be exercised to ensure that such symptoms do not emerge. Copper, on the other hand, is a known antagonist of zinc during absorption in the GI tract. The study findings did not reveal any negative correlation between serum copper and zinc levels, although the literature suggests that copper absorption is enhanced during zinc deficiency, which may have been responsible for the high proportion of participants with normal serum copper levels.[18] Furthermore, the findings of a meta-analysis showed that elevated serum levels of copper were associated with decreased serum zinc levels in bladder, breast, colon, and prostate cancers,[19] suggesting that further investigation is warranted in patients with terminal cancer.

The present study did not distinguish between GI cancers directly involved in the absorption and loss of ETEs from the GI tract, and non-GI cancers. However, our findings suggest that patients with GI cancers may exhibit low levels of ETEs, and this possibility warrants further investigation.

CONCLUSIONS

Serum TTR and Alb levels are used as indices of nutrition and cachexia and were below the respective reference ranges in all terminal cancer patients who participated in the present study, indicating malnutrition. In contrast, many patients showed CRP levels exceeding the reference range and indicative of chronic inflammation. Furthermore, many patients were found to be deficient in ETEs such as iron and zinc, with serum levels below the respective reference ranges. Our findings show that ETEs offer potentially useful markers of cachexia. Measurement of these ETEs on admission may be helpful and can guide appropriate nutritional management. Furthermore, zinc levels correlated with cachexia-related proteins, suggesting an influence on prognosis-defining factors.

Conflict of interest: The authors have no conflict of interest with any corporate or commercial organization involved in the present study.

REFERENCES

1) Shenkin A. The key role of micronutrients. Clin. Nutr. 2006; 25: 1–13.
2) Giovannucci E and Chan AT. Role of vitamin and mineral supplementation and aspirin use in cancer survivors. J. Clin. Oncol. 2010; 28: 4081–4085.
3) Khursheed J. Zinc: An essential trace element for parenteral nutrition. Gastroenterology 2009; 137: S7–S12.
4) Cabal-Manzano R, Bhargava P, Torres-Duarte A, et al. Proteolysis-inducing factor is expressed in tumours of patients with gastrointestinal cancers and correlates with weight loss. Br. J. Cancer 2001; 84: 1599–1601.
5) Khan S and Tisdale MJ. Catabolism of adipose tissue by a tumour-produced lipid-mobilising factor. Int. J. Cancer 1999; 80: 444–447.
6) Goda F, Inukai M, Okuyama H, et al. The feasibility study of the necessity of supplementations of trace elements in healthy elderly subjects. J. JSPEN 2010; 25: 823–829.
7) Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol. 2011; 12: 489–495.
8) Ito A, Higashiguchi T and Oyanagi H. Home parenteral nutrition in Japan. Home Parenteral Nutrition. 2nd ed. 2015. CABI, Boston, p54–62.
9) Tisdale MJ. Pathogenesis of cancer cachexia. J. Support. Oncol. 2003; 1: 159–168.
10) Evans WJ, Morley JE, Argilés J, et al. Cachexia: A new definition. Clin. Nutr. 2008; 27: 793–799.
11) Radbruch L, Elsner F, Trottenberg P, et al. Clinical practice guidelines on cancer cachexia in advanced cancer patients with a refractory cachexia. Aachen, Department of Palliative Medicine/European Palliative Care Research Collaborative; 2011.
12) Murai M, Higashiguchi T, Futamura A, et al. Interleukin-8 and clinical symptoms can be prognostic indicators for advanced cancer patients with cachexia. Fujita Med. J. 2020; 6: 117–121.
13) McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: A decade of experience in patients with cancer. Cancer Treat. Rev. 2013; 39: 534–540.
14) Miura T, Matsumoto Y, Hama T, et al. Glasgow prognostic score predicts prognosis for cancer patients in palliative settings: A subanalysis of the Japan-prognostic assessment tools validation (J-ProVal) study. Support. Care Cancer 2015; 23: 3149–3156.
15) Miura T, Amano K, Shirado A, et al. Low transthyretin levels predict poor prognosis in cancer patients in palliative care settings. Nutr. Cancer 2018; 70: 1283–1289.
16) King JC and Cousins RJ. Zinc. In: Modern Nutrition in Health and Disease, 10th ed. 2006. Lippincott Williams & Wilkins, Philadelphia, p286–299.
17) Tapiero H and Tew KD. Trace elements in human physiology and pathology: Zinc and metallothioneins. Biomed. Pharmacother. 2003; 57: 399–411.
18) Yanagisawa H. Zinc deficiency and clinical practice. J. Jpn. Med. Assoc. 2003; 129: 613–616.
19) Pierre L, Lucie S, Jean LC, et al. The multifaceted roles of copper in cancer: A trace metal element with dysregulated metabolism, but also a target or a bullet for therapy. Cancer 2020; 12: 3594.