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The usefulness of zinc administration and the importance of measuring serum zinc concentrations

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Abstract

Zinc is an essential trace element that plays various and pivotal roles in the human body. Therefore, zinc homeostasis is tightly regulated by ion channels and zinc transporters, including the Zrt-Irt-like protein (ZIP) and zinc transporter (ZnT) families. Disrupting this zinc homeostasis often causes zinc deficiency in various diseases (e.g., liver cirrhosis, chronic renal diseases, and inflammatory bowel diseases) and contributes to the underlying pathological conditions. Although the amount of zinc in the serum accounts for only approximately 0.1% of the total zinc in the body, this serum concentration is usually measured and analyzed in these diseases. Measuring the serum concentration is the only way to assess pathological conditions and evaluate the effect of zinc treatment when specific symptoms are not observed. For liver diseases, zinc concentrations decrease with the progression of fibrosis in patients with chronic liver diseases (CLDs); thus, many investigators treat these patients with zinc preparations. Supplementation with zinc for not only a short time but also a long time was effective, and the zinc serum concentration is a useful index for achieving good prognosis. Several studies revealed that it is important to maintain a serum zinc concentration of more than70 μg/dl after zinc supplementation, and a quantity of zinc of approximately 90 mg/day is needed in patients with liver cirrhosis.

Key words: Zinc, HCC, liver function, zinc concentrations

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Abbreviations used in this paper:

ZIP; Zrt-Irt-like protein, ZnT; zinc transporter, CLD; chronic liver diseases, ZF; zinc finger, TFs; transcription factors, SOD; superoxide dismutase, OTC; ornithine transcarbamylase, GDH; glutamate dehydrogenase, HCC; hepatocellular carcinoma

Introduction

Zinc is an essential trace element that has been reported to play various and pivotal roles in the human body. It acts not only as a cofactor for the functions of over 300 enzymes but also as an essential component for zinc finger (ZF)-containing transcription factors (TFs), copper/zinc superoxide dismutase (SOD) and various proteins involved in DNA repair [1-3]. Notably, in the

liver, zinc is needed for the activation of many enzymes, such as ornithine transcarbamylase (OTC) and glutamate dehydrogenase (GDH), which are utilized in the urea cycle or glutamine synthetase cycle. To fulfill this crucial role, zinc homeostasis is tightly regulated by ion channels and zinc transporters, including the Zrt-Irt-like protein (ZIP) and zinc transporter (ZnT) families [4, 5]. Put simply, the amount of zinc in the body is adjusted via absorption in the digestive tract and excretion in feces. Disrupting this zinc homeostasis often causes zinc deficiency in various diseases (e.g., liver cirrhosis, chronic renal diseases, and inflammatory bowel diseases, **Figure 1**), which contributes to the underlying pathological conditions [6-9]. Zinc deficiency was observed even in half of healthy volunteers, which might show that intake of zinc is not enough in this modern life.

Although the amount of zinc in the serum accounts for only approximately 0.1% of the total zinc in the body, this serum concentration is usually measured and analyzed in many cases. Another zinc index is needed to accurately evaluate total zinc in the body, and some attempts have been made, such as alkaline phosphatase and OTC. In current clinical settings, however, the serum zinc concentration is the only way to assess total zinc in the body. In an animal study, the serum zinc concentrations correlated with the zinc content in hepatic tissue [10]. The serum zinc concentration correlated with the pathologies of specific diseases in many studies [11]. Therefore, the serum zinc concentration may be a useful index for assessing pathological conditions and evaluating the effect of treatments. Furthermore, determining how to adjust systemic serum zinc concentrations through dietary supplementation may provide useful information for the management of specific diseases. The aim of this review is to summarize the evidence in the most recent literature with a focus on the serum zinc concentration and chronic liver diseases (CLDs). Moreover, this review also discusses the relationships between zinc supplementation and the improvement of pathological conditions.

Mechanisms of zinc deficiency in chronic liver diseases

Vallee RL et al. first reported in 1956 the occurrence of marked hypozincemia in patients with severe cirrhosis [12]. This hypozincemia was confirmed by many investigators, and three reasons have been proposed [13, 14]. First, patients with CLD have an inadequate dietary intake of zinc [15]. Second, absorption of zinc is also impaired in these patients because of portal

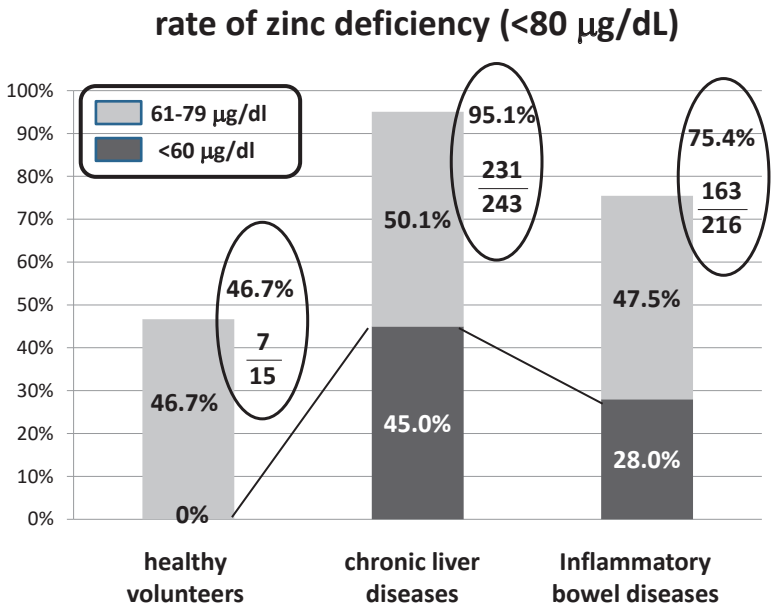

Figure 1. Rate of zinc deficiency (<80 μg/dl) including latent zinc deficiency (60-79μg/dl) in healthy volunteers and patients with various diseases

This data was obtained by single center, retrospective cohort study. Those who had health checkup were recruited in this study as healthy volunteers if they had no diseases. Serum zinc concentrations were examined among patients with chronic liver diseases and inflammatory bowel diseases on their first visit to our hospital or when they were diagnosed on the first time. Gray bar displays the ratio of latent zinc deficiency. Chronic liver diseases; chronic hepatitis (164 cases) and liver cirrhosis (79 cases), Inflammatory bowel diseases; ulcerative colitis (208 cases) and Crohn's diseases (8 cases).

hypertension [16]. Third, urinary excretion of zinc is increased, and greater excretion was observed in patients taking diuretics [14, 17]. The serum zinc concentration gradually decreased with the progression of CLD by these mechanisms and this fact was reported by Iwata K [18]. This is consistent with our results (**Figure 2** and **Table 1**). As described above, zinc homeostasis is tightly regulated by many ion channels and zinc transporters, but it cannot be maintained in patients with CLD. When the zinc concentration decreases, the expression of ZIP4 usually increases. Additionally, its intracellular localization is changed to absorb a large amount of zinc and augment the amount of zinc in the body [19]. It is unknown whether these mechanisms are disrupted or whether zinc absorption is interrupted more than the regulation of zinc transporters. The zinc concentration ultimately decreases with the progression of fibrosis in patients with CLD.

Effect of zinc supplementation

As zinc helps to activate some enzymes in the urea cycle, many investigators have focused on improving hepatic encephalopathy through the administration of supplemental zinc. Reding et al. first reported that oral zinc supplementation improved hepatic encephalopathy in 22 cirrhotic patients in a double-blind randomized trial [20]. The effect of taking 600 mg zinc acetate per day for 7 days was evaluated in that study. Katayama et al. also showed the importance of zinc supplementation; in that study,

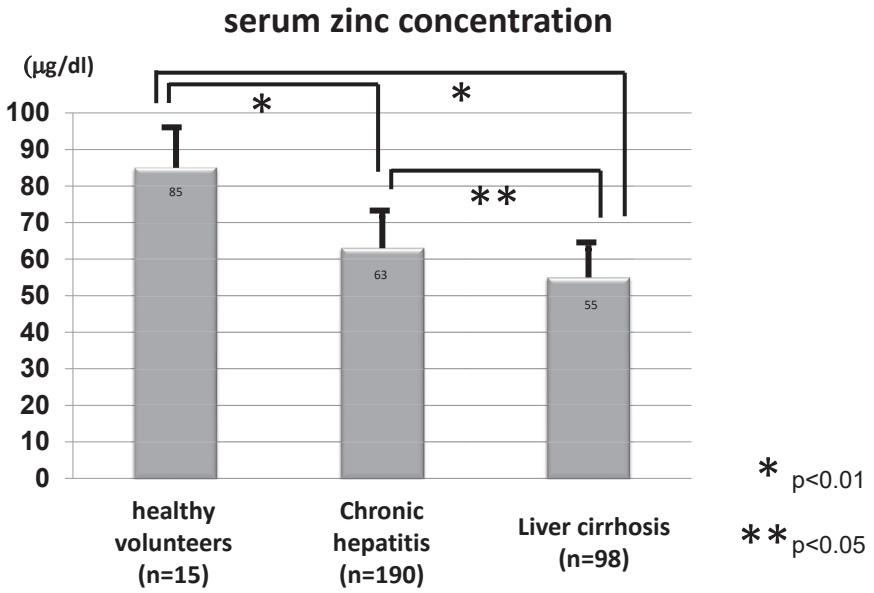

Figure 2. **Serum zinc concentrations in healthy volunteers, and patients with CLD or liver cirrhosis**
This data was obtained by single center, retrospective cohort study. Clinical profiles were shown in the **Table 1**. Some patients were diagnosed by liver biopsy, but others were clinically judged by the criteria proposed by Enomoto H [26]. Serum zinc concentrations decreased with the progression of fibrosis.

Table 1. **Clinical profile of healthy volunteers and patients with chronic liver diseases**

	Healthy volunteers	Chronic hepatitis	Liver cirrhosis
the number of patients	15	190	98
mean age (years)	48.9 ± 10.4	66.4 ± 12.6	73.2 ± 9.3
gender (F/M)	11 / 4	62 / 128	18 / 80
Zn (μg/dl)	84.9 ± 10.8	63.2 ± 8.9	55.3 ± 8.6
T.Bil (mg/dl)	0.7 ± 0.6	1.2 ± 1.8	1.6 ± 1.8
Albumin (g/dl)	4.2 ± 0.4	4.0 ± 0.5	3.3 ± 0.8
PT activity (%)	98 ± 17	89 ± 10	72 ± 11
platlet count (10^4/ul)	23.2 ± 6.5	18.3 ± 8.5	12.8 ± 10.2

3 months of zinc acetate supplementation was shown to be effective and safe for the treatment of hyperammonemia in patients with cirrhosis [21]. A systematic review and meta-analysis of the use of zinc in patients with hepatic encephalopathy showed a significant improvement in psychological tests in those undergoing zinc therapy [22]. However, many of these studies have focused on short-term zinc administration, and few studies have explored the long-term effects of zinc administration in patients with CLD. We found that zinc administration improves liver function and decreases the cumulative incidence of HCC in patients with CLD over the course of long-term follow-up [6]. Taken together, supplementation with zinc for not only a short time but also a long time was effective for patients with CLD. The longer patients are treated with zinc, the more adverse events occur. The adverse drug reactions were reported to be digestive symptoms, such as abdominal discomfort, pain, and vomiting, and elevation of pancreatic enzymes (amylase, lipase), deficiency of cupper, pancytopenia, anemia, and neurological disorders [23]. The next question is how long zinc preparations need to be treated and whether it is possible to discontinue this treatment.

Serum zinc concentration as an evaluation after zinc supplementation

A zinc index is needed to accurately evaluate total zinc in the body after zinc supplementation, but the serum zinc concentration is currently the only way to assess total zinc in the body as described above. Subjects administered zinc demonstrated higher serum zinc concentrations at week 8 than subjects administered a placebo [23], and these levels decreased to the basal level after discontinuation of treatment (unpublished data). Continuous administration of zinc is needed to maintain higher serum zinc concentrations. However, is it necessary to do to achieve good clinical outcomes? There are almost no papers exploring the appropriate concentration of zinc, but Takamatsu reported that a serum zinc concentration of more than 72 μg/dl after zinc supplementation was needed for the suppression of fibrosis in 57 patients with CLD [24]. In our study, patients in the zinc-treated group were divided into 4 groups according to their zinc concentration at 6 months after the start of the zinc treatment, and we investigated the liver function and the cumulative incidence of hepatocellular carcinoma (HCC) in these groups. Finally, to obtain a better prognosis, patients with CLD must maintain a serum zinc concentration of more than 70 μg/dl after zinc supplementation [6]. Our results are almost consistent with Takamatsu's report, and both of these studies showed that it is important to increase and maintain a certain level of zinc for better prognosis.

The relationship between the dose of zinc administered and the serum zinc concentration

The final question was how much zinc is needed to reach the appropriate zinc concentration. Almost all investigators who have performed zinc analysis confirmed the importance of zinc administration in clinical settings, but the dose of zinc was quite different in these studies. Katayama used 150 mg/day of zinc to treat patients with liver cirrhosis and hyperammonemia. Nobelzin® capsules (50 mg) were administered after each meal three times a day, and each capsule contains 167.84 mg zinc acetate dehydrate including 50 mg of zinc (Nobelpharma Co., Ltd., Tokyo, Japan) [21]. In Himoto's study, they treated patients with CLD with polaprezinc (150-225 mg/day including 34-51 mg/day of zinc), and Takamatsu also used 150 mg/day of polaprezinc (34mg of zinc) [24, 25]. The minimum required quantities of zinc may depend on individual differences; thus, we focused on patients whose zinc administration doses were changed. Zinc sulfate contains an equivalent of 60-120 mg of zinc, while polaprezinc contains 17-51 mg of zinc. Some physicians began to treat patients with zinc sulfate, but this treatment was discontinued or the initial dose was reduced because of adverse events. Other physicians started polaprezinc but changed to zinc sulfate to increase the zinc concentration. In fifteen patients, zinc sulfate was changed to polaprezinc, and in nine patients, polaprezinc was changed to zinc sulfate. The clinical backgrounds of these patients are shown in **Table 2**. The serum zinc concentration increased to 62.0 μg/dl from 51.3 μg/dl after the polaprezinc therapy, and it remained low during the administration of polaprezinc (**Figure 3a**, left panel, mean period of the administration of polaprezinc was 9 months). It increased to more than 90 μg/dl after the change to zinc sulfate in these patients. The administration quantity of zinc increased from 37.6 mg to 98.6 mg (**Figure 3a**, right panel). This tendency was also observed in another 9 patients. The serum zinc concentration increased to more than 90 μg/dl after zinc sulfate therapy, and it was maintained during the administration of zinc sulfate (**Figure 3b**, left panel, mean period of administration was 26 months). The concentration decreased to less than 70 μg/dl after the change to polaprezinc in these patients. The administration quantity of zinc also decreased from 97.7 mg to 41.6 mg (**Figure 3b**, right panel). This finding shows that the zinc concentration decreased according to the quantity of zinc administration. This study revealed that most patients with liver cirrhosis needed to take more than 90 mg/day of zinc to reach a zinc concentration over 70 μg/dl. These findings suggest that 30-40 mg/day of zinc

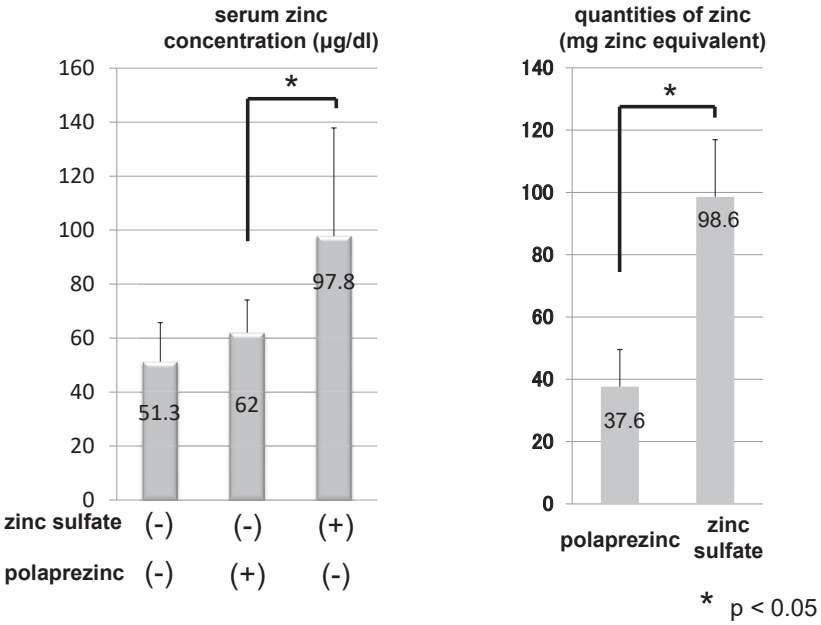

Figure 3a. **(Left panel) Serial changes in serum zinc concentrations before and after the administration of polaprezinc and after the exchange of polaprezinc to zinc sulfate (Right panel) Change in the administration quantity of zinc during the administration of polaprezinc or zinc sulfate**

Fifteen patients were administered polaprezinc. Then, it was discontinued, and they were treated with zinc sulfate.

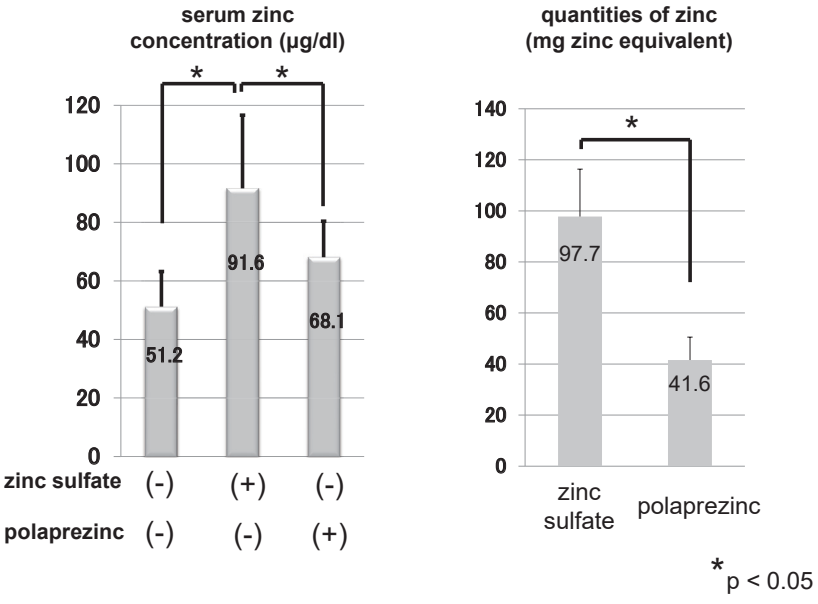

Figure 3b. **(Left panel) Serial changes in serum zinc concentrations before and after the administration of zinc sulfate and after the exchange of zinc sulfate to polaprezinc (Right panel) Change in the administration quantity of zinc during the administration of zinc sulfate or polaprezinc**

Nine patients were administered zinc sulfate. Then, it was discontinued and they were treated with polaprezinc.

Table 2. Clinical profiles of 24 patients with chronic liver diseases whose administration doses of zinc were changed

Fifteen patients were administered polaprezinc, and then, it was changed to zinc sulfate. Nine patients were administered zinc sulfate, and then, it was changed to polaprezinc.

	PZ→zinc sulfate	zinc sulfate→PZ
	Figure 3a	Figure 3b
the number of patients	15	9
mean age (years)	74.9 ± 5.4	75.6 ± 7.3
gender (F/M)	11 / 4	6 / 3
Zn (μg/dl)	51.3 ± 14.4	51.2 ± 12.0
T.Bil (mg/dl)	1.3 ± 0.7	1.2 ± 1.8
Albumin (g/dl)	3.1 ± 0.8	3.3 ± 0.8
PT activity (%)	68.4 ± 17.1	68.8 ± 10.2
platlet count (10^4/ul)	10.5 ± 4.5	11.8 ± 10.2
BTR (BCAA/tyrosine ratio)	3.49 ± 1.91	2.26 ± 0.61
Chronic hepatitis/liver cirrhosis	8 / 7	4 / 5

PZ: polaprezinc

in polaprezinc is not enough to attain optimal zinc levels in patients with CLD, especially in those with advanced fibrosis. Taken together, sufficient amount of zinc is needed to maintain a serum zinc concentration of more than 70 μg/dl.

Conclusion

This review article highlights the effect of zinc supplementation and the importance of the serum zinc concentration. Six years have passed since zinc preparation was approved for patients with zinc deficiency. The target recipients have recently been patients with certain diseases. In particular, patients with CLD can be treated with zinc; this treatment results in the improvement of pathological conditions, including hepatic encephalopathy and cancer development. We next focused on how to treat these conditions and who should be treated. The serum zinc concentration is one of the most useful and accurate indices to evaluate total zinc in the body and to assess the effects of zinc treatment. Many investigators have already confirmed that the administration of zinc is effective in improving pathological conditions in many diseases, but the ideal zinc concentration or administration dose is unclear. For the treatment of CLD, the zinc concentration should be more than 70 μg/dl to obtain good prognosis, and more than 90 mg/day of zinc should be administered to reach that concentration. In each disease, such as inflammatory bowel disease or chronic renal disease, the ideal concentration of zinc might be different and should be clarified in the future. In any case, we can treat zinc preparations in patients with zinc deficiency, which can improve pathological conditions. Zinc should be used appropriately based on numerous studies and firm evidences.

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