

Zinc Deficiency and Clinical Practice —Validity of Zinc Preparations—

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Zinc is an essential trace element and serves as the active center of approximately 300 enzymes. Therefore, zinc deficiency may be associated with a variety of clinical features such as hypogeusia, hyposmia, growth retardation, dermatitis, alopecia, gonadal hypofunction, abnormal pregnancy, susceptibility to infections, delayed wound healing, impaired glucose tolerance, and increased carcinogenesis. Zinc deficiency was reported to be on the increase in the Nagano Study conducted from 2003 to 2005. Zinc therapy is classified into two categories, zinc-supplementary and -specific treatments. Ordinarily, zinc-supplementary therapy is carried out for the symptoms and diseases caused by zinc deficiency. On the other hand, zinc-specific therapy is applied to obtain copper- and iron-chelating, antifibrotic, and antidiabetic effects. The availability of zinc-specific therapy is now confirmed in humans and animals. Hereafter, the safety of zinc therapy needs to be examined further.

Key words—physiologic functions of zinc; zinc deficiency; zinc therapy

INTRODUCTION

Zinc, an essential trace element, is known to serve as the active center of approximately 300 enzymes.^{1,2)} Therefore a variety of symptoms and diseases are caused by zinc deficiency.¹⁾ In outpatient clinics, the number of patients with complaints of an abnormal sense of taste and/or olfaction has been on the increase. It has been estimated that approximately 240000 patients with such complaints are registered annually and that approximately 30% of these patients have dietary zinc deficiency.³⁾

It has been recently reported that the amount of zinc ingested per day may be insufficient relative to the daily requirement in some groups of individuals, particularly children, elderly people, young women on weight-reducing diets, and other groups.^{1,4)} These individuals may develop a subclinical or clinical deficiency of zinc.^{1,4)} Approximately 20% of the inhabitants (approximately 5000 people) of Nagano prefecture were in a zinc-deficient state and approximately 10% of them were in a zinc-subdeficient state when serum zinc levels were examined from 2003 to 2005 (Nagano Study),⁵⁾ suggesting a similar trend in all Japanese.

On the other hand, zinc-supplementary therapy for the symptoms and diseases derived from zinc deficiency and zinc-specific therapy for Wilson disease, chronic hepatitis type C, diabetes mellitus, *etc.* have been recently attempted.^{1,4)} Particularly, some orally active Zn (II) complexes have dramatically ameliorated the pathophysiology of diabetes mellitus and metabolic syndrome in animal experiments.⁶⁾

This paper reviews the physiologic functions of zinc and recent trends in zinc therapy for a better understanding of the clinical features of zinc deficiency and zinc therapy.

PHYSIOLOGIC FUNCTIONS OF ZINC

Zinc serves as the active center of approximately 300 enzymes such as carbonic anhydrase, alkaline phosphatase, superoxide dismutase (SOD), *etc.* (Table 1).^{1,2)} Consequently, zinc contributes to growth, development, wound healing, immune functions, skin metabolism (particularly collagen synthesis), maintenance of central nervous functions, maintenance of retinal functions (participation in vitamin A metabolism), senses of taste and olfaction, saliva secretion, production and activity of sperm, prevention of carcinogenesis and aging (participation in scavenging superoxides), maintenance of gonadal functions and pregnancy (participation in the synthesis and secretion of sex hormones), glucose meta-

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Table 1. Zinc Enzymes and Their Functions

Zinc enzyme	Function
Carbonic anhydrase, peptidase, alcohol dehydrogenase, alkaline phosphatase, polymerase, superoxide dismutase, angiotensin-converting enzyme, collagenase, δ -aminolevulinic acid anhydrase, protein kinase C, phospholipase C, aspartate transcarbamylase, nucleotide phosphorylase (5'-nucleotidase), RNase, <i>etc.</i>	Cell division, Nucleic acid metabolism, Coenzymes

Table 2. Symptoms and Diseases Caused by Zinc Deficiency

Anorexia
Growth retardation
Skin symptoms
• Extension from mucocutaneous junctions (mouth, eyes, anus, <i>etc.</i>) to the periphery
• Bullous or pustular dermatitis, erosive eczema, hyperkeratosis, skin atrophy, decubitus ulcer
Alopecia/baldness
Gonadal hypofunction
Delayed wound healing
Susceptibility to infections (compromised immune function)
Hypogeusia/hyposmia
Pica
Depression/emotional instability
Ataxia
Dementia
Reduced glucose tolerance
Disorder of lipid metabolism
Increased incidence of cataracts
Disturbed dark adaptation (night blindness)
Increased incidence of ischemic heart disease
Increased carcinogenesis
Abnormal pregnancy

bolism (participation in the synthesis and action of insulin), and lipid metabolism.^{1,4} As shown in Table 2, a variety of symptoms and diseases are therefore seen in a zinc-deficient state.

The author has recently reported that zinc deficiency may lead to the exacerbation of tubulointerstitial nephropathy caused by ureteral obstruction through enhancing the action of the potent vasoconstrictors endothelin-1 and the renin-angiotensin system^{7,8} and to the development of hypertension *via* increasing the oxidative stress associated with the production of

superoxide.⁹

ZINC THERAPY AND PREPARATIONS

Zinc therapy is classified into the two categories, supplementary and specific treatments. Ordinarily, zinc preparations used for zinc therapy are inorganic zinc compounds (zinc sulfate, zinc acetate, zinc gluconate), polaprezinc (Promac, Zeria Pharmaceutical Co., Ltd.), and zinc supplements.^{1,4}

Zinc-supplementary Therapy Usually, zinc-supplementary therapy is carried out for a variety of symptoms and diseases caused by zinc deficiency (Table 2). In daily medical practice, hypogeusia derived from zinc deficiency is a good indication for zinc-supplementary therapy.^{1,4} The disorder of gustation is caused not only by dietary zinc deficiency but also by secondary zinc deficiency associated with medication (approximately 170 drugs) and diseases (Table 3). In recent years, it has been shown that in addition to hypogeusia, zinc-supplementary therapy is also markedly effective in decubitus ulcers and glossalgia.⁵ In the near future, zinc-supplementary therapy will become widespread as a therapeutic treatment for decubitus ulcers and glossalgia. Table 4 summarizes of the therapeutic course of anorexia, hypogeusia, decubitus ulcers, glossitis-like symptoms, oropharyngeal symptoms, glossalgia, and cheilalgia.

Recently, a shortage of dietary zinc ingestion has been indicated.^{1,3,4} As a result, health promotion foods, supplements, and over-the-counter (OTC) preparations containing zinc have been widely utilized for the prevention of carcinogenesis, aging, arteriosclerotic disease, and a decrease in immune function as well as for health promotion.^{1,4} The amounts of health promotion foods, supplements, and OTC preparations taken per day often contain 20–30 mg of zinc. Most investigators have reported that these foods and preparations result in an increase in im-



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Table 3. Major Causes of Zinc Deficiency

1. Inadequate intake
1) Low zinc-containing diets : foods poor in animal protein (vegetarians)
2) Loss of zinc during food processing (desalting during production of artificial milk, <i>etc.</i>)
3) Prolonged intravenous alimentation Enteral alimentation
4) Shortage of nutrient intake
2. Malabsorption
1) Congenital : acrodermatitis enteropathica (very rare)
2) Acquired
(1) Ingestion of absorption inhibitors : sodium polyphosphate, phytic acid, edible fibers, Cu, Fe, Ca, Mn
(2) Malabsorption syndrome : liver dysfunction, pancreatic dysfunction, inflam- matory bowel disease, short bowel syndrome
(3) Drugs with chelating activity (approximately 170 drugs) : EDTA, penicillamine, captopril, <i>etc.</i>
3. Excessive loss
1) Loss into digestive fluid : pediatric intractable diarrhea, intestinal fistula, gas- trointestinal disease associated with diarrhea
2) Increased urinary elimination : liver cirrhosis, diabetes mellitus, renal disease, hemo- lytic anemia, intravenous alimentation, enhanced catabolism (surgery, trauma, infection, <i>etc.</i>), diuret- ics, sodium polyphosphate
3) Others : burns, hemodialysis
4. Increased demand : pregnancy, neonates (premature babies), enhanced anabolism (during intravenous alimentation, <i>etc.</i>)
5. Unexplained : congenital thymus defect, Down's syndrome

immune function and in the activity of SOD scavenging the free radical superoxide,¹⁰ indicating the validity of zinc preparations used for supplementary therapy.

Ordinarily, zinc-supplementary therapy is continued for 3 or 4 months. If initiated within 6 months after the onset of zinc deficiency, the response rate to this therapy (the percentage of cases in which the therapy is effective or markedly effective) is 70% or higher. The response rate decreases if the therapy is started later than 6 months following the onset of zinc deficiency. In cases responding to therapy, zinc supplementation sometimes must be continued for approximately 6 months or longer.^{1,4)}

It is important to take zinc toxicity into account in zinc-supplementary therapy. The lowest adverse effect level of zinc is approximately 50–60 mg per day.¹⁰ Thus a daily zinc dose of approximately 30 mg would be relatively safe in zinc-supplementary therapy.

Zinc-specific Therapy

Inhibitory effects of zinc preparations on the absorption of copper and iron The absorption of copper and iron is suppressed in the small intestine when 50–60 mg of zinc is ingested daily.^{10,11} This inhibitory effect on copper absorption may be attributed to increased synthesis of the trace metal-binding protein metallothionein in the small intestinal cells. Consequently, copper, exhibiting a stronger binding affinity with metallothionein than zinc, is stored in the small intestinal cells.¹¹ On the other hand, it is considered that the inhibitory effect on iron absorption may be due to the antagonistic action by zinc in the process of iron absorption by the small intestinal mucosa because the mechanism responsible for the absorption of zinc and iron is similar.¹¹ Zinc prepa-

Table 4. Effects of Zinc-supplementary Therapy on Symptoms and Diseases Due to Zinc Deficiency

	Time to recovery	Therapeutic course/effectiveness
Anorexia	A few days to 1 week	Dramatic
Hypogeusia	A few weeks to 1 month or longer	Sluggish ; intractable tendency in long-term cases
Decubitus ulcer	A week to a few weeks in the early stage ; 3 months or longer in the advanced stage (with debridement if necessary)	Healing in most cases
Glossitis-like symptoms (no local findings in most cases) Oropharyngeal symptoms	A few days to 1 month	Earlier amelioration than hypogeusia
Glossalgia	A few weeks to a few months	Intractable tendency
Cheilalgia		More intractable than glossalgia

rations are prescribed to reduce copper accumulation in Wilson disease (Fig. 1). Zinc preparations are also used as iron-chelating agents in the treatment of chronic hepatitis type C with the complication of iron accumulation (Fig. 2).

Antifibrotic effects of zinc preparations It is well known that zinc participates in collagen metabolism. As shown in Fig. 3, zinc decreases the activity of lysyloxidase involved in the bridge forma-

tion of collagen in the process of collagen synthesis.¹¹⁾ As a result, zinc exerts antifibrotic effects through the inhibition of cross-linking of collagen peptides.¹¹⁾ Zinc also serves as the active center of the collagen degradation enzymes, collagenase and matrix metalloprotease.^{1,4,11)} Thus zinc promotes collagen degradation through the action of these enzymes. In recent years, zinc preparations, particularly polaprezinc, have been used as an antifibrotic agent in

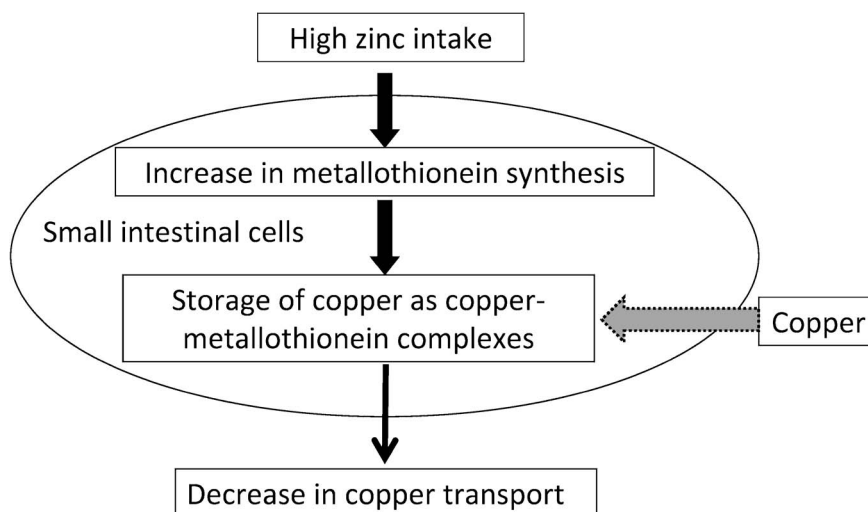


Fig. 1. Wilson Disease

Ordinarily, large amounts of inorganic zinc compounds (1.0–1.5 mg Zn/kg/day) are used in combination with copper-chelating agents such as D-penicillamine, thus reducing a dose of copper-chelating agents.

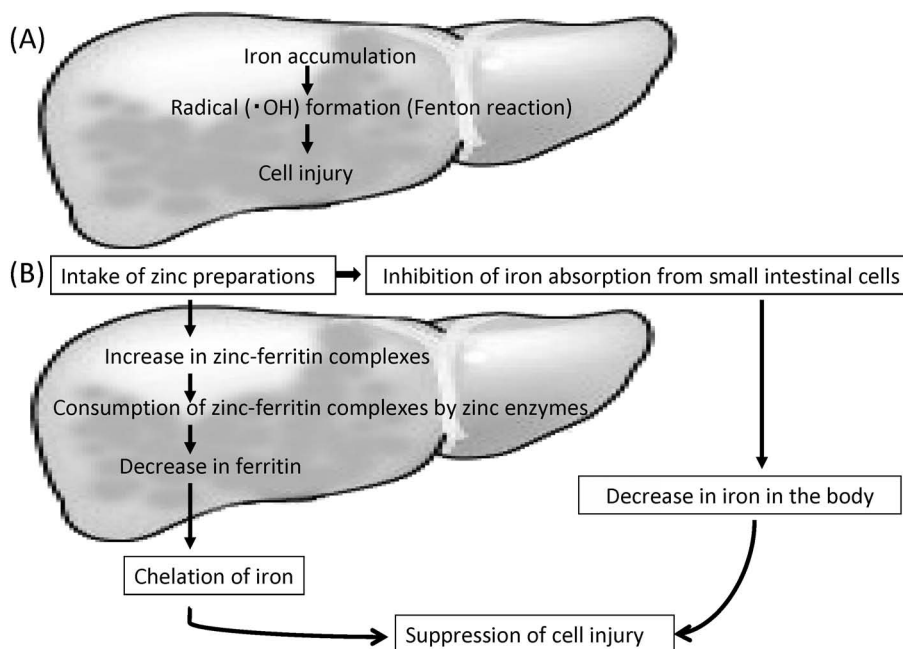


Fig. 2. Potential Mechanisms Responsible for Cell Injury Chronic Hepatitis Type C (A): resulting from iron accumulation; (B): the suppressive effect of zinc preparations on cell injury.

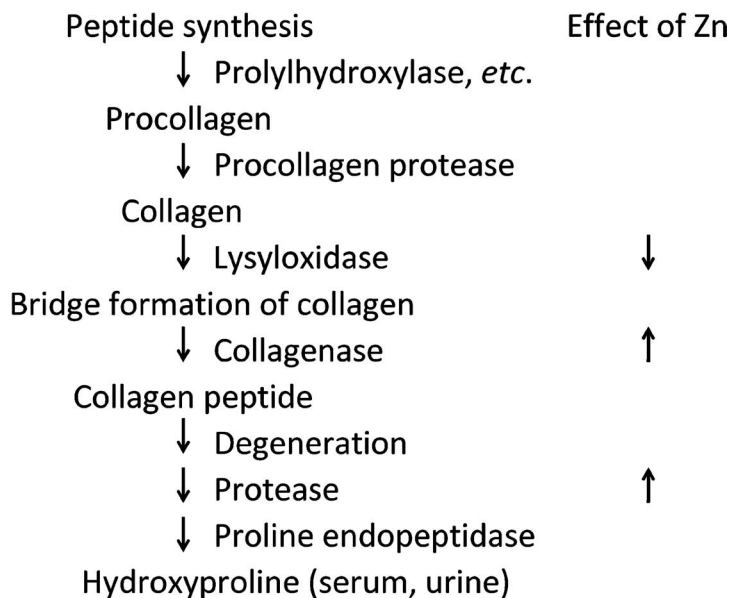


Fig. 3. Collagen Metabolism and Inhibitory Effects of Zinc Preparations on Collagen Accumulation
 ↑, increase in activity; ↓, decrease in activity.

Ligands	Chemical structures of zinc(II) complexes
N ₂ O ₂	<p>Zn(Pa)₂ Zn(6mpa)₂ Zn(6mpa-ma)₂ Zn(Thr)₂ Zn(Ala)₂</p>
S ₂ O ₂	<p>Zn(ptp)₂ Zn(THIA-Me)₂</p>
N ₄	<p>Zn(ampy)₂ Zn(aepy)₂</p>
O ₄	<p>Zn(vc)₂ Zn(car)₂ Zn(mal)₂ Zn(alx)₂ Zn(tanm)₂ Zn(hkt)₂</p>

Fig. 4. Zinc(II) Complexes Exhibiting Antidiabetic Effects
 Cited from Reference 12) with slight modification.

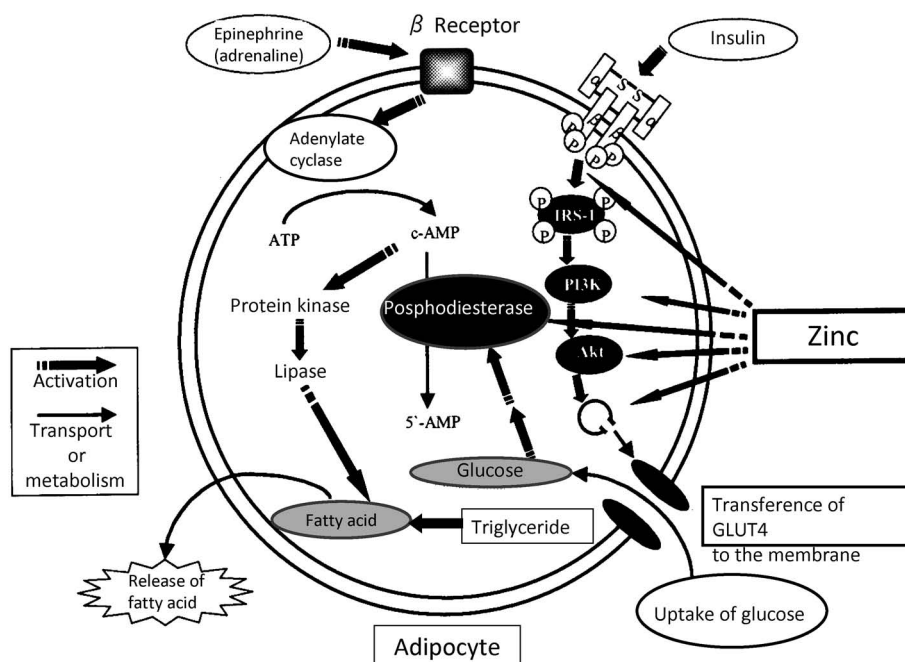


Fig. 5. Mechanisms Responsible for the Insulin-like Effects Caused by Zinc(II) Complexes
Cited from Reference 12) with slight modification.

patients with chronic hepatitis type C.¹¹⁾

Insulinomimetic effects of zinc(II) complexes

Zinc not only contributes to the synthesis and action of insulin^{1,4)} but also generates insulin-like effects in an insulin-independent manner.^{6,12)} The group of Sakurai *et al.* has synthesized Zn(II) complexes exhibiting hypoglycemic effects (Fig. 4).^{6,12)} Zn(II) complexes have high bioavailability and powerful hypoglycemic activity.^{6,12)} Daily oral administrations of the novel Zn(II) complex Zn(tanm)₂ for 4 weeks in obesity-linked type 2 diabetic KKA^y mice significantly ameliorated hyperglycemia, impaired glucose tolerance, insulin resistance, hypertension, obesity, and hyperleptinemia.⁶⁾ Surprisingly, Zn(tanm)₂ normalized decreased plasma adiponectin levels in KKA^y mice.⁶⁾ These observations demonstrate that the orally active Zn(II) complexes, particularly Zn(tanm)₂, may be beneficial in the treatment of obesity-linked type 2 diabetes and metabolic syndrome. The mechanisms based upon the development of insulin-like activity by Zn(II) complexes are shown in Fig. 5.¹²⁾ However, further studies are required to achieve the clinical application of Zn(II) complexes as novel antidiabetic agents.

Other conditions treated with zinc preparations

Zinc-deficient anemia, Crohn disease, ulcerative colitis, rheumatoid arthritis, osteoporosis, *etc.* are

other conditions for which zinc therapy may be potentially beneficial.

CONCLUSION

The physiologic functions of zinc, clinical symptoms and diseases associated with zinc deficiency, and zinc therapy are not yet fully understood. In addition, no optimum dose levels for zinc therapy have been established. Thus further studies on zinc functions and the safety of zinc therapy are required.

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