Zinc Deficiency and Clinical Practice

JMAJ 47(8): 359–364, 2004

Hiroyuki YANAGISAWA

Associate Professor, Department of Hygiene and Preventive Medicine, Saitama Medical School

Abstract: In recent years, the number of patients visiting outpatient clinics with complaints of abnormal sense of taste or olfaction has been on the increase. It has been estimated that about 30% of these patients may have dietary zinc deficiency. This deficiency is more likely to develop among children whose daily requirements of zinc are greater, among elderly people whose dietary consumption of nutrients is poor, and among young women who are often on diets for weight reduction. Zinc deficiency may be associated with features such as hypogeusia, hyposmia, growth retardation, dermatitis, alopecia, compromised gonadal function, susceptibility to infections, and delayed wound healing. At present, measurement of the serum zinc level is considered to be the most reliable means of diagnosing zinc deficiency. It has been proposed that if the serum copper level were also measured, then the ratio of the serum copper to zinc level (serum copper/zinc ratio) can be used as reference information for diagnosing zinc deficiency. For the treatment of zinc deficiency, zinc replacement therapy at a daily zinc dose of about 30 mg is considered to be relatively safe. However, further study of the safety and adverse effects of zinc replacement therapy is necessary.

Key words: Zinc; Essential trace elements; Deficiency

Introduction

The number of patients visiting outpatient clinics with complaints of abnormal sense of taste or olfaction (most frequently reduced or abnormal sense of taste) has been on the increase.[1,2] It has been estimated that about 140,000 new patients with such complaints are registered annually,[2] and that about 30% of these patients have dietary zinc deficiency.[1,2] Zinc is known to serve as the active center of about 300 enzymes, and is an essential trace element in humans (Table 1).[1]

It has been reported that the amount of zinc ingested per day may be insufficient relative to the daily requirement in some groups of individuals (children, elderly people, young women on weight-reducing diets, and some other groups). These individuals may develop quasi-deficiency or true deficiency of zinc.[1,2] In

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 129, No. 5, 2003, pages 613–616).

Table 1 Zinc and Its Functions

Essential trace element	Target	Function
Zinc	Carbonic anhydrase, peptidase, alcohol dehydrogenase, alkaline phosphatase, polymerase, superoxide dismutase (SOD), angiotensin-converting enzyme, collagenase, δ-aminolevulinic acid anhydrase, protein kinase C, phospholipase C, aspartate transcarbamylase, nucleotide phosphorylase (5'-nucleotidase), RNase, etc.	Cell division, nucleic acid metabolism, co-enzymes

Source: Yanagisawa, H.: Clinical aspects of zinc deficiency. *The Journal of the Japan Medical Association* 2002; 127(2): 261–268.

Table 2 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)
   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: Phytic acid, edible fibers
      (2) Malabsorption syndrome: Liver dysfunction, pancreatic dysfunction, inflammatory bowel disease, short bowel syndrome
      (3) Drugs, chelating agents: EDTA, penicillamine
3. Excessive loss
   1) Loss into digestive fluid: Child intractable diarrhea, intestinal fistula, gastrointestinal disease associated with diarrhea
   2) Increased urinary elimination: Liver cirrhosis, diabetes mellitus, renal disease, hemolytic anemia, intravenous alimentation, enhanced catabolism (surgery, trauma, infection, etc.), diuretics, sodium polyphosphate
   3) Others: Burns, hemodialysis
4. Increased demand
   Pregnancy, neonates (premature babies), enhanced anabolism (during intravenous alimentation, etc.)
5. Unexplained
   Congenital thymus defect, Mongolism

*Underlined = particularly important

Source: Yanagisawa, H.: Clinical aspects of zinc deficiency. *The Journal of the Japan Medical Association* 2002; 127(2): 261–268. Yanagisawa, H. *et al.*: Zinc — Extensive blood and urine biochemistry and immunological tests (2). *Japanese Journal of Clinical Medicine* 1999; 57(extra issue): 282–286.

this paper, we shall briefly discuss the etiology, clinical symptoms, and the methods of diagnosis and treatment of zinc deficiency, a condition that has recently drawn much attention.

Etiology

Zinc deficiency can be divided into congenital and acquired types of zinc deficiency. Acrodermatitis enteropathica, an inherited abnormality of zinc absorption, is rare. Most cases are induced by post-natal factors (Table 2).[1] Acquired zinc deficiency is often attributable to extreme deficiency of nutrients including zinc, or extremely unbalanced diets (insufficient ingestion of animal proteins rich in zinc).

The most frequent causes of zinc deficiency are prolonged high-calorie parenteral therapy and enteral nutrition. Long-term high-calorie parenteral therapy inevitably induces zinc deficiency. To avoid its occurrence, IV solution additives containing 5 trace elements (iron,

Table 3 Symptoms and Diseases Caused by Zinc Deficiency

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

Source: Yanagisawa, H.: Clinical aspects of zinc deficiency. *The Journal of the Japan Medical Association* 2002; 127(2): 261–268.

zinc, copper, manganese, and iodine), that have recently become available commercially (including Elemenmic® (Ajinomoto Pharma Co., Ltd.) and Mineralin® (Nihon Pharmaceutical Co., Ltd. and Takeda Chemical Industrials, Ltd.), may be used. The use of these additives has reduced the apparent incidence of zinc deficiency. Although these 5 trace elements are also contained in preparations used for enteral nutrition, zinc deficiency can develop if the amount of zinc in the diet is insufficient relative to the requirement, or if the patients have such conditions as malabsorption, diarrhea, or intestinal fistula. Furthermore, zinc deficiency can be induced by continued use of low-mineral purified foods (minerals are lost during purification), foods containing additives with chelating activity (sodium polyphosphate, phytic acid, or EDTA [which is also used as a drug]), and drugs which can disturb the sense of taste (about 170 such drugs are known, and many of them have chelating activity[2]).[1,2]

Regarding the relationship of zinc deficiency with age, the deficiency is more likely to develop during childhood, when the daily requirement of zinc is higher, in adult women (especially young women on weight-reducing diets), and in elderly people whose dietary consumption of nutrients is poor. In a survey in the United States, a reduced serum level of zinc was seen in 2–3% of the population.[1]

Clinical Symptoms

While the symptoms of zinc deficiency are common irrespective of the causative factors (Table 3),[1] they may vary depending on the severity of zinc deficiency.

Mild cases of zinc deficiency may present with such features as a reduced sense of taste, reduced sperm counts, reduced serum testosterone level, and non-fat weight loss. Moderate cases of zinc deficiency, which may develop in association with deficient nutrient intake, unbalanced nutrition, chronic liver disease, chronic renal disease, malabsorption syndromes, may present with growth retardation, delayed gonadal development, skin abnormalities, anorexia, somnolence, reduced dark adaptation, delayed wound healing, hypogeusia, and hyposmia. In severe zinc deficiency, which may be associated with acrodermatitis enteropathica, prolonged high-calorie parenteral therapy, or penicillamine therapy, features such as bullous or pustular dermatitis, diarrhea, balding, mental abnormalities (depression, etc.), and recurrent infections due to compromised immune function may be seen.

Of the aforementioned symptoms, subjects with hypogeusia, in particular, and hyposmia

Table 4 Possible Conditions Suggested by Serum Zinc Levels and Countermeasures

Serum zinc level ($\mu g/dl$)	Possible conditions	Countermeasures
300–700	Acute intoxication (reported)	First aid
160–299	Intoxication or secondary elevation due to excessive intake or hemodialysis	Cause identified and removed Follow-up
84–159	Normal range	
60–83	Zinc deficiency (Table 2) Physiological fluctuation (Table 5) Variation caused by drugs, etc. (Table 5)	Cause identified and removed as needed Dietary therapy (ingestion of zinc rich food) Zinc replacement as needed
Below 59	Deficiency (Table 2)	Cause identified and removed Dietary therapy (ingestion of zinc rich food) Zinc replacement
Below 30	Definite deficiency (acrodermatitis enteropathica, prolonged high-calorie parenteral therapy) (Table 2)	Zinc replacement

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are often encountered at outpatient clinics. In hospitals for elderly patients, erosive eczema spreading from mucocutaneous junctions (e.g., mouth, eye, anus, etc.) towards the periphery, as well as bullous or pustular dermatitis, are often noted as the first symptoms of zinc deficiency. In recent years, it has been suggested that zinc deficiency may be associated with carcinogenesis, senility, and the onset or progression of some lifestyle-related diseases (Table 3).[1)]

The authors recently reported that zinc deficiency may lead to exacerbation or progression of renal disease (especially diseases of the glomeruli) through inducing the expression of endothelin-1 (a potent vasoconstrictor) which stimulates the renin-angiotensin system,[4–6)] and also to exacerbation of hypertension through increasing the oxidative stress associated with the production of superoxides.[4,7)]

Diagnosis

Many methods of diagnosis of zinc deficiency have been attempted.[3)] At present, measurement of the serum (plasma) zinc level (Table 4), and confirmation of a deficient state by administering a zinc load are considered to be the most reliable methods of diagnosing zinc deficiency.[1–3)] However, since the intracellular level of zinc is higher than its serum level, it is quite plausible that the serum zinc level may not faithfully reflect the nutritional state of an individual. It must be borne in mind that the serum zinc level may fall at the lower end of the normal range even in the presence of zinc deficiency. The serum zinc level may also show circadian variations (high level in the morning and low level in the afternoon) and changes related to the contents of meal. It can also be affected by some drugs (Table 5). Therefore, when checking for zinc deficiency on the basis of the serum zinc levels, in addition to consideration of the clinical symptoms, it would be essential to take these aforementioned factors also into account.

Zinc is absorbed primarily from the small

Table 5 Changes in Serum Zinc Levels

Condition	Change
Fasting	Increase
Food ingestion	Decrease (2–3 hours later)
Stress	Increase
Ingestion of marine products	Increase (oyster, etc.)
Neonates and infants	Decrease
Pregnancy	Decrease (gradually)
Drugs	
Glucocorticoids	Decrease
Thiazides	Increase
Loop diuretics	Increase
Disulfirams	Increase
Clofibrates	Decrease
Oral contraceptive pills	Decrease

Source: Yanagisawa, H.: Clinical aspects of zinc deficiency. *The Journal of the Japan Medical Association* 2002; 127(2): 261–268.
Yanagisawa, H. *et al.*: Zinc — Extensive blood and urine biochemistry and immunological tests(2). *Japanese Journal of Clinical Medicine* 1999; 57(extra issue): 282–286.

intestine. In the presence of zinc deficiency, absorption of copper is enhanced.[1)] As a result, a reduced serum zinc level, elevated serum copper level, and an elevated serum copper/zinc ratio are noted in the presence of zinc deficiency.[1,2)] Thus, measurement of the serum copper level may be a helpful auxiliary test in the diagnosis of zinc deficiency.[1,2)] Like the authors, Tomita *et al.* proposed that diet therapy and oral zinc replacement therapy must be started in individuals who satisfy all of the following criteria of zinc deficiency: (1) serum zinc level lower than the quasi-deficiency level (Table 4) and (2) serum copper level over 120μg/d*l* as a reference value, i.e., a serum copper/zinc ratio of 1.5 or higher.[2)] Confirmation of the diagnosis using a zinc load is advisable in suspected cases of zinc deficiency in whom the serum zinc level is normal.[1–3)]

Treatment[1,2)] (Table 4)

In cases of zinc deficiency associated with high-calorie parenteral therapy, Elemenmic® or Mineralin® (trace element preparations) may be added to parenteral nutritional formulas. If zinc deficiency is seen during enteral nutrition, zinc compounds such as zinc sulphate, zinc gluconate, or zinc picolinate may be added to the enteral preparations. If oral ingestion is possible, these zinc compounds may be administered orally mixed with juices, or in the form of enterosoluble capsules.

In adults, a daily zinc dose of 150–200 mg (as the zinc compound) is usually sufficient. In Japan, the anti-ulcer agent polaprezinc (Promac®, ZERIA Pharmaceutical Co., Ltd.) is commercially available as a zinc preparation. The daily dose of polaprezinc includes 34 mg of zinc load, which is sufficient for the treatment of zinc deficiency, although only its use in the treatment of gastric ulcer is covered by the National Health Insurance in Japan.

Recently, health promotion foods and OTC drugs containing zinc have been marketed in Japan. The amounts of these foods or drugs taken per day often contain 20–30 mg of zinc. Therefore, it is possible to use these foods or OTC drugs for zinc replacement therapy. Usually, zinc replacement therapy is continued for 3–4 months. If initiated within 6 months after the onset of zinc deficiency, the response rate to this therapy (the percentage of cases where the therapy is effective or markedly effective) is 70% or higher. The response rate decreases, especially in elderly people, if the therapy is started later than 6 months after the onset of zinc deficiency. In cases responding to therapy, the zinc replacement therapy may sometimes have to be continued for about 6 months.

Conclusion

The etiology, clinical symptoms, and methods of diagnosis and treatment of zinc deficiency

are described in this paper. Although no optimum dose level for zinc replacement therapy has been established, daily doses of about 30 mg zinc seem to be relatively safe. It would be desirable for additional studies on the safety and adverse effects of zinc therapy to be conducted, and for new zinc preparations for the treatment of zinc deficiency to be developed.

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