

Micronutrient Deficiency Syndrome: Zinc, Copper and Selenium

Jee Hyun Lee, M.D.

Department of Pediatrics, Hallym University Kangnam Sacred Heart Hospital, Seoul, Korea

Nutrients are defined as not only having nutritive values of participating in the metabolism and building the structures of cells but also being safe for human body. Nutrients are divided into two types, macronutrient and micronutrient, according to the proportion of the human body. Commonly, micronutrients include trace elements (trace mineral) and vitamins (complex organic molecules). It is difficult to demonstrate micronutrient deficiency because the symptoms are varied and laboratory analyses are limited. Since parenteral nutrition became an established therapy, micronutrient deficiency syndromes are being identified more frequently and emphasize the importance of a complete nutritional support. In this article, we review various specific trace element deficiency states such as zinc, copper, and selenium and briefly discuss the use of dietary supplements. (*Pediatr Gastroenterol Hepatol Nutr* 2012; 15: 145~150)

Key Words: Zinc, Copper, Selenium, Dietary supplements, Child

INTRODUCTION

Nutrients are defined as having nutritive values (they participate in the metabolism building structures of cells) and being presumed to be safe to the human body also. Nutrients are classified into three macronutrients (carbohydrate, protein and fat) and the rest of the unclassified micronutrients are required in very small quantities, yet pose important influence on metabolism and health [1]. Micronutrients are of two types, trace elements (inorganic elements) and vitamins (complex organic mole-

cules). These micronutrients are necessary for the optimal utilization of the three macronutrients. Trace elements contribute less than 0.01% to body weight and a human nutritional requirement has been established for iron, iodine, zinc, copper, chromium, selenium, molybdenum, manganese, and cobalt [2]. Cotzias defined essential trace elements as having the following five characteristics: 1) present in healthy tissues of all living things, 2) maintain a constant tissue concentration, 3) withdrawal leads to reproducible functional abnormalities, 4) addition of the element prevents abnormalities, 5)

Received : September 7, 2012, Revised : September 10, 2012, Accepted : September 12, 2012

Corresponding author: Jee Hyun Lee, M.D., Department of Pediatrics, Hallym University Kangnam Sacred Heart Hospital, 1, Singil-ro, Yeongdeungpo-gu, Seoul 150-950, Korea. Tel: +82-2-829-5145, Fax: +82-2-829-5358, E-mail: izzih@medimail.co.kr

Copyright © 2012 by The Korean Society of Pediatric Gastroenterology, Hepatology and Nutrition

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

biochemical change is prevented or cured with clinical abnormality [3].

Biological effect of any trace element depends on the dose; problems may result from intakes that are too low or too high.

The etiology of trace element deficiency is varied. First, inadequate intake situations are associated with increased requirements, losses during food processing, poor bioavailability, local deficiencies in the geochemical environment, protein energy malnutrition, and synthetic diets including intravenous feeding. Variations in bioavailability are major factors that determine the adequacy of dietary intake of some trace elements [4]. It is especially important for infants who depend on one major food staple. Second, other circumstances are associated with prematurity (small reservoirs), impairment of intestinal absorption, and inborn errors of trace element metabolism [5]. Recently, the increasing use of synthetic diets in medical practice, including those used in intravenous feeding, has provided some of the most dramatic examples of acquired trace element deficient states. Deficiencies of zinc, copper, chromium, molybdenum, and selenium have been documented in association with long-term intravenous feeding [6].

Quantitative measurement of trace elements which are present in a very small amount is difficult. Laboratory analysis and the detection of trace elements use the atomic absorption spectrophotometry. Even when the analytic data are accurate, interpretation of the data frequently becomes a problem. Recently, hair analysis was introduced and misused as a diagnostic tool. Currently, the application of chemical analysis of hair in clinical practice is extremely limited [7,8].

In this article, we review various trace element deficiency states such as zinc, copper, and selenium and briefly discuss the use of dietary supplements.

ZINC DEFICIENCY

Diet zinc deficiency syndrome showing hypo-

gonadism, anemia, and growth retardation was reported in 1961 [9]. Acrodermatitis enteropathica, an autosomal recessive disorder of gastrointestinal zinc absorption, resulted in severe acro-orificial dermatitis and diarrhea in infants [10]. After the 1990s, the importance of zinc as an essential nutrient for humans was documented through large scale trials [11-13].

Clinical features of zinc deficiency

The spectrum of clinical manifestations varies from poor appetite and mild dermatitis to life threatening diseases including growth arrest, intractable diarrhea, recurrent infection, and delayed sexual maturation [14]. Patients with acrodermatitis enteropathica show abrupt cessation of weight gain and recovery after zinc supplementation [15]. Diarrhea is one of the frequently and early occurred symptoms in zinc deficiency as well as worsens the zinc-deficiency state by losing endogenous zinc. The skin lesions have a characteristic distribution of primarily localizing in the extremities and adjacent to the body orifices. Most commonly, the rashes are erythematous, vesiculobullous, and pustular. Increased susceptibility of bacterial and fungal infection associated with immune dysregulation, behavioral abnormality and cognitive impairment were also some of the notable features [16].

Etiologic factors in zinc deficiency

An absolute dietary deficiency is rare in the general population with a normal diet but special situations such as long term parenteral nutrition and synthetic diet lacking zinc can cause zinc deficiency. Zinc deficiency has been well documented in premature and low birth weight infants who need a high intake for rapid postnatal growth. Acrodermatitis enteropathica, a rare genetic disease of a defect in the zinc uptake protein can result in severe and extreme cases. Although an inadequate zinc intake may cause zinc depletion, inhibitors of zinc absorption, such as dietary phytate, along with marginal intake are suscep-

tible to zinc deficiency state. Consuming a traditional Korean diet largely based on grains and vegetables may contribute to the risk of marginal zinc deficiency in Korea [17]. The risk of zinc deficiency is increased in certain disease states; fat malabsorption, enteritis, cystic fibrosis, celiac disease, diabetes mellitus, liver disease, nephrosis, and drugs that cause excessive zinc excretion [18].

Diagnosis of zinc deficiency

Most of the clinical features are nonspecific and vague in mild to moderate zinc deficient state but acro-oral skin lesions in severe deficiency are relatively characteristic. There is no reliable way of assessing zinc status and laboratory parameters are of only limited value in the diagnosis of zinc deficiency. Plasma zinc concentrations are maintained in the range between 80 and 120 $\mu\text{g/dL}$ and serum zinc levels have been reported to be higher than the plasma level [19]. However, hypozincemia is not always reflected in zinc deficiency. There may be other causes of decreased plasma zinc level such as pregnancy and infection. Leukocyte zinc concentrations are reliable but difficult to measure [20,21]. Hair analysis of zinc has very limited value in infants and children. Hair zinc level is decreased in mild zinc deficiency, but in acute and severe deficient states, hair growth is arrested and the remaining hair may show normal zinc level [19]. Serum alkaline phosphatase activity is diminished in severe zinc deficiency. Because of the limitations of currently available laboratory indices in the detection of mild zinc deficiency, the most reliable approach is the demonstration of the effects of zinc supplementation under adequately controlled conditions [2].

Treatment of zinc deficiency

In mild zinc deficiency, zinc supplementation is 1 mg/kg/day up to a maximum of 20 to 30 mg/day. Severely zinc deficient states like acrodermatitis enteropathica can be treated with 40 to 60 mg/day [2]. In the parenteral nutrition state, maintenance requirements in adults are 2 mg/day, in infants

100 $\mu\text{g/kg/day}$, and in premature infants 300 $\mu\text{g/kg/day}$ have been recommended [22]. Ongoing losses due to diarrhea, fistula, burn state may increase the requirement [19].

COPPER DEFICIENCY

Copper is an essential nutrient for humans and a component of many enzymes that regulate various metabolic processes. Copper deficiency is rare in humans. Since the first report on hypochromic anemia as a manifestation of copper deficiency in 1964, copper deficiency has been documented in patients with prolonged severe malabsorption, severe malnutrition, and parenteral nutrition without copper supplementation, and in premature infants [23]. Copper is absorbed mostly in the small intestine and distributed in high concentrations in the liver and brain. Copper is transported to the liver and incorporated into ceruloplasmin and then released into the peripheral tissue. Copper is mostly excreted through bile [24].

Clinical features of copper deficiency

The hematologic findings of copper deficiency are neutropenia and hypochromic, normocytic anemia that is unresponsive to iron supplementation. Various bony changes are noted including osteoporosis, subperiosteal bone formation, and fibrosis of the epiphysis. Other clinical features are observed in premature infants including cardiac disease, arthritis, loss of hair and skin pigmentation, and neurologic abnormalities that mimic vitamin B12 deficiency [2,24-26].

Etiologic factors in copper deficiency

Copper deficiency is associated with malnutrition and reports have shown that copper supplementation to infants recovering from malnutrition improved their growth rates. The term neonates gain sufficient hepatic copper stores during the third trimester of pregnancy. So premature infants of low birth weight have very little copper at birth. The incidence of copper deficiency in very low birth

weight infants has been declining due to the use of copper-fortified premature infant formula [27]. Other causes of copper deficiency have been observed in parenteral nutrition without copper supplementation [28], intestinal malabsorption syndrome, chronic diarrhea, and high intake of zinc and iron [2].

Diagnosis of copper deficiency

The diagnosis of copper deficiency should be suspected in the presence of suggestive etiologic states with hypochromic anemia unresponsive to iron treatment, neutropenia and osteopenia. The laboratory findings of plasma copper and ceruloplasmin are decreased in the copper deficient state, but we should keep in mind that these parameters are also influenced by other factors (protein malnutrition, acute inflammation, gestation age) [2]. The serum copper level does not always correlate with copper balance and therefore serum copper and ceruloplasmin levels should not be used as the sole indicators of copper status. Copper levels in hair and nail are not reliable. The enzyme levels of cytochrome oxidase and superoxide dismutase in erythrocytes have been investigated as an index of copper status but have not been used in practical applications [29].

Treatment of copper deficiency

Copper deficient infants are treated with 2 to 3 mg/day of 1% copper sulfate solution [2]. Copper supplementation in parenteral nutrition between 0.5 and 1.5 mg/day was suggested for adults and 20 μ g/kg/day was suggested for pediatric patients [30]. Excessive copper supplementation via parenteral nutrition may cause hepatotoxicity especially in premature infants [31].

SELENIUM DEFICIENCY

Selenium is used for the synthesis of selenocysteine to be incorporated into mammalian proteins. About 25 selenoproteins have been revealed for their own functions of antioxidant enzymes, puta-

tive antioxidant proteins, and other metabolic functioning enzymes [32]. A wide spectrum of biochemical functions of selenium leads to broad clinical manifestations.

Clinical features of selenium deficiency

The earliest recognized selenium deficiency was Keshan disease in China, an endemic cardiomyopathy reported in geochemically selenium poor areas [33]. Cardiomyopathy or skeletal myopathy, loss of hair, and macrocytic anemia are manifested in cases of long term parenteral nutrition or synthetic oral diet without selenium supplementation [34-36].

Diagnosis of selenium deficiency

Plasma selenium that reflects the amount of selenoproteins (mainly selenoprotein P) is widely used. With trauma or systemic inflammation, the plasma selenium level may be decreased, requiring careful interpretation [37]. Glutathione peroxidase, the second largest proportion contributed to total selenoproteins, can respond rapidly to the changes in selenium intake [38]. The measurements of selenium in hair and nails are limited in terms of reliability and complexity of analysis.

Treatment of selenium deficiency

The optimal treatment for selenium deficiency has not been determined. Selenium supplements should be added routinely from the beginning of the course of parenteral nutrition [34]. Recommendation for intravenous selenium intake is 2 μ g/kg/day for preterm and term infants, as well as for children [2].

DIETARY SUPPLEMENTS

Neutraceutical is a concentrated matrix of bioactive agent from food and a dietary supplement that makes us fitter and healthier. The purposes of using dietary supplements to children are as follows: 1) optimization of growth and development, 2) correcting the dietary inadequacy, and 3)

prevention and treatment of childhood diseases [39]. When dietary supplements are used in children, there are a few special considerations. First, each nutrient competes for absorption in the body, thus high dose supplementation with single nutrients can be toxic and dangerous. Diet supplementation may lead to interference with other drugs or medications. Second, nutraceutical products are sometimes inconstant in dosage listed on the label and can be contaminated. Third, there is a lack of research or established evidence of intake for children [40]. The most commonly used dietary supplements are multivitamins and minerals to make up for the inadequacies in a child's diet. There are no benefits for healthy children with a regular adequate diet. However, if the dietary intake of nutrients is chronically inadequate, the use of multivitamin and mineral supplements may be advisable. Physicians should obtain the history of supplement use from pediatric patients and monitor the adverse reactions.

CONCLUSION

Micronutrients are provided ideally in a normal diet, because the gut normally acts to regulate absorption in response to demand. However, in special situations, such as synthetic diet, long term parenteral nutrition with incomplete formula, and lack of reservoirs (preterm infants, low birth weight, and malnutrition state), trace element deficiency can be developed. The diagnosis of micronutrient deficiency syndrome is difficult but careful analysis of clinical manifestations and laboratory findings are essential and sufficient. Infants are vulnerable toward micronutrient deficiency syndrome because of their rapid postnatal growth, low initial stores and ingestion of foods with low concentration of micronutrients. And supplements of nutraceuticals in children are required careful consideration for a thorough understanding of overdose toxicity and interference with other nutrients and drugs for proper treatment of patients with micronutrient deficiency.

REFERENCES

1. Maclean WC Jr, Lucas A. Pediatric nutrition: a distinct subspecialty. In: Walker WA, Watkins JB, Duggan C, eds. *Nutrition in pediatrics: basic science and clinical applications*. 3rd ed. Hamilton: BC Decker Inc., 2003:1-5.
2. Krebs NF, Hambidge M. Trace elements. In: Walker WA, Watkins JB, Duggan C, eds. *Nutrition in pediatrics: basic science and clinical application*. 3rd ed. Hamilton: BC Decker Inc., 2003:86-110.
3. Mertz W. Review of the scientific basis for establishing the essentiality of trace elements. *Biol Trace Elem Res* 1998;66:185-91.
4. Hurrell RF. Influence of vegetable protein sources on trace element and mineral bioavailability. *J Nutr* 2003;133:2973S-7S.
5. Mziray-Andrew CH, Sentongo TA. Nutritional deficiencies in intestinal failure. *Pediatr Clin North Am* 2009;56:1185-200.
6. Hardy G, Menendez AM, Manzanares W. Trace element supplementation in parenteral nutrition: pharmacy, posology, and monitoring guidance. *Nutrition* 2009;25:1073-84.
7. Sriram K, Lonchyna VA. Micronutrient supplementation in adult nutrition therapy: practical considerations. *JPEN J Parenter Enteral Nutr* 2009;33:548-62.
8. Kosanovic M, Jekanovic M. Quantitative analysis of toxic and essential elements in human hair. Clinical validity of results. *Environ Monit Assess* 2011;174:635-43.
9. Prasad AS, Halsted JA, Nadimi M. Syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism and geophagia. *Am J Med* 1961;31:532-46.
10. Moynahan EJ. Letter: Acrodermatitis enteropathica: a lethal inherited human zinc-deficiency disorder. *Lancet* 1974;2:399-400.
11. Brown KH, Pearson JM, Rivera J, Allen LH. Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2002;75:1062-71.
12. Goldenberg RL, Tamura T, Neggers Y, Copper RL, Johnston KE, DuBard MB, et al. The effect of zinc supplementation on pregnancy outcome. *JAMA* 1995;274:463-8.
13. Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, et al. Prevention of diarrhea and pneumonia by zinc supplementation in children in develop-

- ing countries: pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. *J Pediatr* 1999;135:689-97.
14. Van Wouwe JP. Clinical and laboratory assessment of zinc deficiency in Dutch children. A review. *Biol Trace Elem Res* 1995;49:211-25.
15. Ackland ML, Michalczyk A. Zinc deficiency and its inherited disorders -a review. *Genes Nutr* 2006;1:41-9.
16. Prasad AS. Zinc: an overview. *Nutrition* 1995;11(1 Suppl):93-9.
17. Kim J, Paik HY, Joung H, Woodhouse LR, Li S, King JC. Effect of dietary phytate on zinc homeostasis in young and elderly Korean women. *J Am Coll Nutr* 2007;26:1-9.
18. Jeejeebhoy KN. Human zinc deficiency. *Nutr Clin Pract* 2007;22:65-7.
19. Jeejeebhoy K. Zinc: an essential trace element for parenteral nutrition. *Gastroenterology*. 2009;137(5 Suppl):S7-12.
20. Lin CN, Wilson A, Church BB, Ehman S, Roberts WL, McMillin GA. Pediatric reference intervals for serum copper and zinc. *Clin Chim Acta* 2012;413: 612-5.
21. Liu J, Yuan E, Zhang Z, Jia L, Yin Z, Meng X, et al. Age- and sex-specific reference intervals for blood copper, zinc, calcium, magnesium, iron, lead, and cadmium in infants and children. *Clin Biochem* 2012;45:416-9.
22. Greene HL, Hambidge KM, Schanler R, Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. *Am J Clin Nutr* 1988;48:1324-42.
23. Danks DM. Copper deficiency in humans. *Annu Rev Nutr* 1988;8:235-57.
24. Olivares M, Araya M, Uauy R. Copper homeostasis in infant nutrition: deficit and excess. *J Pediatr Gastroenterol Nutr* 2000;31:102-11.
25. Milne DB. Copper intake and assessment of copper status. *Am J Clin Nutr* 1998;67(5 Suppl):1041S-5S.
26. Desai V, Kaler SG. Role of copper in human neurological disorders. *Am J Clin Nutr* 2008;88:855S-8S.
27. Shah MD, Shah SR. Nutrient deficiencies in the premature infant. *Pediatr Clin North Am* 2009;56: 1069-83.
28. Shike M. Copper in parenteral nutrition. *Gastroenterology* 2009;137(5 Suppl):S13-7.
29. Harvey LJ, McArdle HJ. Biomarkers of copper status: a brief update. *Br J Nutr* 2008;99 Suppl 3:S10-3.
30. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr* 2002;26(1 Suppl): 1SA-138SA.
31. Frem J, Sarson Y, Sternberg T, Cole CR. Copper supplementation in parenteral nutrition of cholestatic infants. *J Pediatr Gastroenterol Nutr* 2010;50:650-4.
32. Rayman MP. Selenium and human health. *Lancet* 2012;379:1256-68.
33. Chen J. An original discovery: selenium deficiency and Keshan disease (an endemic heart disease). *Asia Pac J Clin Nutr* 2012;21:320-6.
34. Shenkin A. Selenium in intravenous nutrition. *Gastroenterology* 2009;137(5 Suppl):S61-9.
35. Bank IM, Shemie SD, Rosenblatt B, Bernard C, Mackie AS. Sudden cardiac death in association with the ketogenic diet. *Pediatr Neurol* 2008;39:429-31.
36. de Berranger E, Colinet S, Michaud L, Cremer R, Fourrier C, Brévière GM, et al. Severe selenium deficiency secondary to chylous loss. *JPEN J Parenter Enteral Nutr* 2006;30:173-4.
37. Burk RF, Hill KE, Motley AK. Plasma selenium in specific and non-specific forms. *Biofactors* 2001;14: 107-14.
38. Nève J. Methods in determination of selenium states. *J Trace Elem Electrolytes Health Dis* 1991;5:1-17.
39. Zeisel SH, Erickson KE. Dietary supplements (nutraceuticals). In: Walker WA, Watkins JB, Duggan C, eds. *Nutrition in pediatrics: basic science and clinical applications*. 3rd ed. Hamilton: BC Decker Inc., 2003:986-96.
40. Zadik Z, Sinai T, Zung A, Golander A, Reifen R. "Functional food" for acceleration of growth in short children born small for gestational age. *J Pediatr Endocrinol Metab* 2010;23:435-41.