

GROWTH AND MINERALS: ZINC

MASAYUKI KAJI, MD

Division of Endocrinology and Metabolism
Shizuoka Children's Hospital
Shizuoka, Japan

YOSHIKAZU NISHI, MD

Department of Pediatrics
Hiroshima Red Cross Hospital
Hiroshima, Japan

INTRODUCTION

Zinc (Zn) is well known to be essential for somatic growth of children. Zinc has a close relationship with the endocrine system; it sustains normal growth, secondary sex characteristics, reproductive function and thyroid function. Therefore, Zn deficiency causes not only growth retardation, but also delayed sexual maturation, hypogonadism, and thyroid dysfunction. In this paper, the effects of Zn on childhood growth are presented.

Highlights In This Issue

- Summary Highlights: ESPE-LWPES Joint Meeting...page 8
- Measured versus Reported Parental Height.....page 10
- Apnea in PWS Patients on GH Therapypage 10
- Suppression of Agingpage 11
- Motivations for GH/GnRHa Treatment and Psychosocial Functioning.....page 12
- Efficacy of GH During Transition from Adolescence to Adulthood in Patients with GHD ...page 14
- Pituitary GH-secretory Cellspage 14
- Genomic Alterations in Embryonic Stem Cellspage 15

E-Abstracts (Abstracts On-line)

- Cardiovascular Effects of GH in GHD Adults
- Children's Virilization by Testosterone Gels
- Defective Matrix Turnover Causes SEMD-Missouri
- Joint Mobility and T1DM Complications
- Nomenclature for Intersex
- RMRP Gene is an Essential Cell Growth Regulator
- Silver-Russell Syndrome Epimutations
- X-Chromosome Inactivation and Autoimmune Thyroid Disease

From The Editor's Desk

Those of you who have followed this column may be aware of the trials and tribulations of the recent past, as *GGH* faced an uncertain future. But, we are back on track and are delighted to advise you that *GGH* will forge ahead.

This issue brings to an end the era of the long-term sponsorship of *GGH* by Genentech, Inc. They generously supported this educational vehicle since its inception in 1985. On behalf of our readers and Editorial Board I extend our thanks for what they did for the journal. Their support allowed *GGH* to become established and develop into a highly sought-after journal. *Growth, Genetics & Hormones* is read by most pediatric endocrinologists worldwide and other specialists interested in the field of growth.

I am happy to report that we will enjoy an unrestricted educational grant from our new sponsor, INSMED (Glen Allen, Virginia). Thanks to them, we will continue publishing *GGH* as we have done for two decades and you will continue to receive *GGH* on a complementary basis.

While searching for the means to continue *GGH*, I was very motivated by countless colleagues who wrote of the high value they placed on *GGH*; many were willing to pay for a subscription to the journal if needed. I thank all of you who encouraged me, and in this way helped with the task of eliciting funding to serve the educational goals of our colleagues.

The Editorial Board has pledged their time and effort to review the latest advances in the field and grace us with their insightful comments. I am looking forward to a new era of *GGH* and to continue bringing you the most updated reviews and lead articles of interest to the readership. We will continue to enhance the impact of *GGH* and strive to ensure that readers continue to enjoy and treasure it.

Please keep me posted of your needs and recommendations for continuous enhancements. There are multiple journals and other means to stay informed, but none like this journal. Join me in extending your thanks and appreciation to our past sponsor and a heartfelt welcome and thanks to our new sponsor, INSMED, for making this possible.

Respectfully,
Fima Lifshitz, MD
FimaLifshitz@GGHjournal.com

THE ROLE OF ZN ON THE HOMEOSTATIC MECHANISMS THAT AFFECT GROWTH AND GROWTH HORMONE

Zinc ion (Zn^{2+}) is present in high concentrations in the somatotrophs in the anterior pituitary of rats, chiefly localized in the growth hormone (GH) secretory granules, and to a smaller extent in the Golgi apparatus. Particle induced X-ray emission (PIXE) measurements reveal that the content of Zn in the anterior pituitary is significantly different between male and female rats (100.5 ± 7.0 vs 74.2 ± 3.6 [SD] ng/mg dry weight,¹ respectively). On the other hand, in human subjects, the anterior pituitary of women contains more Zn than that of men, but the concentration of Zn in young males is higher than that of young females.² However, the reason for the sex difference of Zn content of the pituitary gland is not clear.

Growth hormone is synthesized and secreted into storage granules before its release from the anterior pituitary. Zinc induces GH dimerization; two Zn ions associate per dimer of GH in a cooperative fashion. The Zn^{2+} -GH dimer is more stable than monomeric GH and the formation of the dimeric complex is considered to be important for storage of GH in secretory granules.³ However, the function of Zn in the release of GH from the somatotrophs is not known.

The mechanism by which Zn deficiency causes growth disturbance is considered controversial. Zinc is required for the activity of more than 200 enzymes (Zn metalloenzymes) in which Zn is located at the active site, including DNA polymerase, RNA polymerase, and thymidine kinase. In general, Zn serves catalytic, co-catalytic, and/or structural functions in metalloenzymes containing this ion. Because these enzymes are important for nucleic acid and protein synthesis and cell division, Zn is considered to be essential for growth. Furthermore, several hundred Zn-containing nucleoproteins are probably involved in the gene expression of various proteins.⁴ The molecular mechanisms by which Zn controls the expression of the insulin-like growth factor (IGF)-I and the growth hormone receptor/growth hormone binding protein (GHR/GHBP) genes remain unsettled.⁵

Zn seems to play a role in the intracellular transduction pathways of several hormones and might activate protein kinase C which could play a role in the transduction of the GH signal.⁶ Zn is an essential component of the "Zn-finger" structures which function as the DNA-binding domains of transcription factors. Zinc-finger is a structure in which an atom of Zn is tetrahedrally coordinated to spatially conserved cysteines and histidines; the Zn atom is absolutely required for binding to DNA.⁷ The presence of Zn in these proteins is essential for site-specific binding to DNA and gene expression.

Zn serves as a strut that stabilizes folding of the domain into a finger loop, which is then capable of site-specific binding to double-stranded DNA.

The Zn-finger loop proteins provide one of the fundamental mechanisms for regulating gene expression of many proteins. It is estimated that there may be approximately 200 to 300 Zn-finger nucleoproteins involved in gene expression. Whether or not Zn deficiency affects these nucleoproteins and gene expression remains to be demonstrated.⁴ Nuclear receptors of several hormones—including steroid hormones and thyroid hormones—contain Zn-finger structures. Therefore, Zn deficiency might cause alterations of these hormonal actions through the dysfunction of Zn-finger proteins.

The presence of a large amount of Zn in bone tissue suggests that this ion also plays an important role in the development of the skeletal system.⁸ Zinc has a stimulatory effect on bone formation and mineralization,⁹ whereas retardation of bone growth is a common finding in various conditions associated with Zn deficiency. Zn is required for the action of alkaline phosphatase (ALP) activity, this enzyme is mainly produced by osteoblasts whose major function is to provide calcium deposition in bone diaphysis. Zinc increases the half-life of ALP activity in human osteoblast-like cells.¹⁰

The administration of both Zn or vitamin D₃ produced a significant increase in bone ALP activity and DNA content, and the effect of vitamin D₃ was synergistically enhanced by the simultaneous treatment with Zn.¹¹ The receptors for 1,25-dihydroxyvitamin D₃ were shown to have two Zn-finger structures at the site of interaction with DNA.¹² One possible function of Zn is to potentiate the interaction of the 1,25-dihydroxyvitamin D₃-receptor complex with DNA.

Zinc directly activates aminoacyl-tRNA synthetase in osteoblastic cells, and it stimulates cellular protein synthesis. Moreover, Zn inhibits osteoclastic bone resorption by suppressing osteoclast-like cell formation from marrow cells. Zinc may act on the process of bone-resorbing factors induced by protein kinase C activation; these are involved in Ca^{2+} signaling in osteoclastic cells.⁹

OPTIMAL AND SUBOPTIMAL ZN NUTRITURE

It has been estimated that the body of the infant newborn contains approximately 60 mg of Zn based on a concentration of 20 μ g/g of tissue.¹³ During growth and maturation, Zn concentration of the human body increases to approximately 30 μ g/g. The adult total body Zn content ranges from about 1.5 g in women to 2.5 g in men.¹⁴ Thus Zn nutrient intake is essential and is particularly important in rapidly growing children, adolescents, as well as pregnant and lactating women.

RDA of Zn in the United States¹⁵

Age	Zn mg/day
normal infants from birth to 12 months of age	5
children 1 to 10 years of age	10
males older than 11 years of age	15
females older than 11 years of age	12
pregnant women	15
lactating women	
first 6 months after delivery	19
second 6 months after delivery	16

The recommended dietary allowances (RDA) of Zn in the United States are listed (Table). The RDA is neither the minimal requirement nor necessarily the optimal level of intake. Rather, the RDA is a safe and adequate level, incorporating margins of safety intended to be sufficiently generous to encompass the presumed variability in requirements among individuals, reflecting the state of knowledge concerning a nutrient, its bioavailability, and variations among the population.¹⁵

Zinc nutriture has been a subject of worldwide concern as a public health problem. The mean and median intakes of Zn reported in 171 studies summarized by the International Atomic Energy Agency ranged from 4.2 to 19 mg/day; the 10th, 50th, and 90th percentiles of intake were 7, 10, and 14 mg/day, respectively.¹⁶ Zinc intake varies with the mode and type of feeding. Zinc intake of breast-fed infants ranged from 1.9 mg/day at 1 month of age to 2.7 mg/day at 6 months, and those of bottle-fed infants were 3.6 and 4.6 mg/day at 1 and 6 months, respectively.¹⁷ However, Zn in human milk is absorbed more efficiently than that in bovine milk. Absorption of Zn was 41 ± 9 % (SD) from human milk, 28 ± 15% from cow's milk, 31 ± 7% from humanized cow's milk formula, 22 ± 11% from cereal-cow's milk formula, and 14 ± 4% from soy formula.¹⁸

Total dietary Zn intake is greatly influenced by food choices. Animal products provide abundant amount of Zn and cereals supply the primary plant source. However Zn intake is correlated with protein intake and is markedly influenced by the protein source. Diets consisting primarily of eggs, milk, poultry, and fish have lower Zn:protein ratios than those composed of shellfish, beef, and other red meats. Similar variations occur in vegetarian diets. Diets with rich Zn:protein ratios are provided by liberal quantities of legumes, whole grains, nuts, and cheese, whereas those with low ratios are contained primarily fruits and vegetables.¹⁹

Zinc absorption is a function of the solubility of Zn compounds at the absorption site and the body status or need. Zinc bioavailability is defined as the fraction of Zn intake that is retained and used for normal physiologic

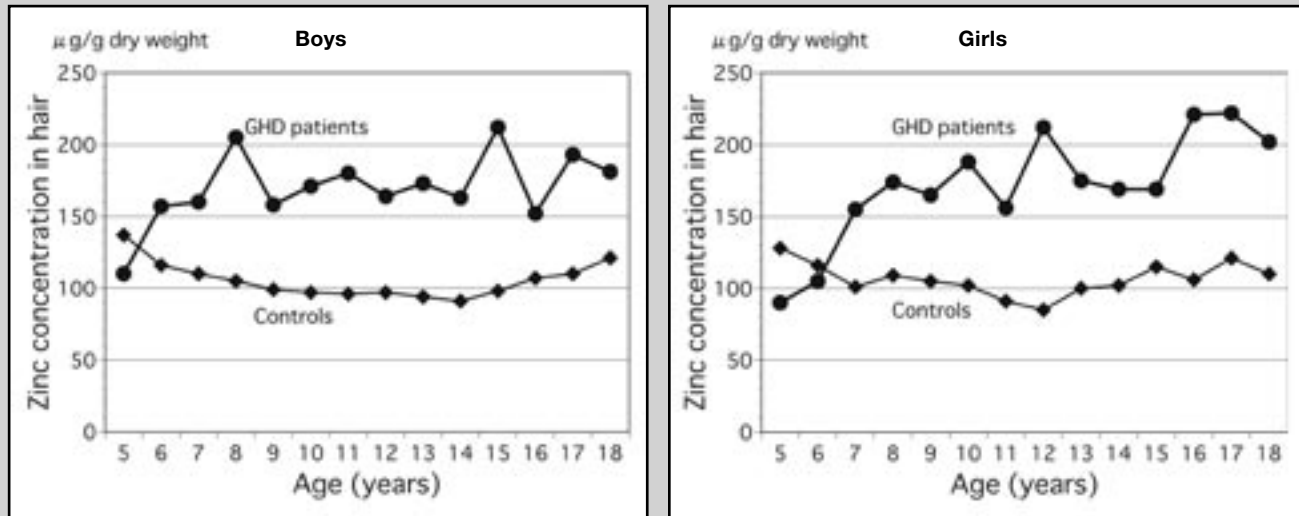
functions. Meats, liver, eggs, and seafood are considered good bioavailable sources of Zn because of the relative absence of compounds that inhibit its absorption, as well as the presence of certain amino acids that improve Zn solubility.¹⁹ For example, the absolute amount of Zn absorbed was about 80% higher when a high meat diet (280 g meat/day) was consumed than with a low meat diet (42 g meat/day).²⁰ On the other hand, whole-grain cereal products and plant proteins, such as soy protein, contain Zn in a less available form. The phytic acid content of plant foods accounts for, at least in part, to the lower availability of Zn from these foods. Dietary fiber is considered to have little or no effect on Zn availability.¹⁹

EFFECTS OF ZN DEFICIENCY AND MARGINAL ZN DEFICIENCY ON GROWTH AND GROWTH HORMONE

It is well known that Zn deficiency causes growth retardation in children and adolescents. Patients with growth retardation caused by Zn deficiency were first described by Prasad et al²¹ in 1963. These patients presented with short stature and hypogonadism; their diets were lacking in protein and were rich in phytate and fiber. They were shown to have Zn deficiency by decreased Zn concentrations in plasma, erythrocytes, and hair. Furthermore, ⁶⁵Zn studies revealed that plasma Zn turnover was greater, the 24-hour exchangeable Zn pool was smaller, and the excretion of ⁶⁵Zn in stool and urine was less in the growth-retarded subjects than in the controls.²¹ The growth velocity was increased and was greater in those who received supplemental Zn than those receiving only an adequate animal protein diet.⁴ Since then, many cases of marginal or moderate growth impairment in children with Zn deficiency as a consequence of an inadequate Zn nutriture have been reported from various regions of the world.^{22,23}

Zinc deficiency is also known to affect GH metabolism and the concentration of GH also influences or is associated with changes in the concentrations of Zn in blood, urine, and other tissues.⁸ In patients with GH deficiency (GHD) the mean plasma Zn concentration was within normal limits before treatment, but was significantly reduced after 4 to 12 months of GH administration. The urinary excretion of Zn was significantly higher than that of controls before treatment and was decreased after GH therapy.²⁴ The average Zn concentration in hair of GHD patients given GH therapy was about 1.7 times higher than that of the controls (Figure), and the hair Zn concentrations of newly diagnosed GHD patients significantly increased after GH administration.²⁵

On the other hand, in patients with acromegaly there was a negative correlation between plasma Zn and serum GH levels, and a positive correlation between urinary Zn excretion and serum GH levels. After hypophysectomy, Zn was observed to increase in plasma and decrease in urine.²⁴ These findings may reflect a negative Zn balance

Mean zinc concentrations in hair of GHD patients and the controls 5-18 years of age.²⁵

and chronic mild Zn deficiency in some GHD patients on long-term GH therapy and in untreated patients with acromegaly. The data suggest that an increased Zn requirement exists during catch-up growth or overgrowth accelerated by GH, and that GH might promote intestinal absorption of Zn and/or promote Zn uptake of hair root cells. It may also be speculated that Zn may be a limiting factor in growth-regulating mechanisms by modulating both GH release and GH action.⁸

Zinc deficiency may adversely affect GH production and/or secretion.²⁶ IGF-I synthesis may also be impaired by Zn deficiency since exogenous GH fails to raise IGF-I levels in Zn-deficient rats.²⁷ Low IGF-I levels in Zn-deprived rats were closely associated with a decreased hepatic IGF-I gene expression and with a diminution of liver GH receptors and circulating GHBP. The decreased hepatic GH receptors and/or GHBP concentrations might be responsible for the decline of circulating IGF-I in Zn-deficient animals.²⁸

The incorporation of labeled thymidine into DNA is also impaired by Zn deficiency. This effect has been detected within a few days of the institution of a Zn-deficient diet in experimental animals, suggesting that DNA biosynthesis⁴ is compromised due to an adverse effect of Zn restriction on the activity of deoxythymidine kinase.²⁹

There have been a few reports concerning the relationship between Zn deficiency and GH secretory insufficiency in humans. We described a 13-year-old Japanese patient with short stature who had partial GH deficiency due to chronic mild Zn deficiency.²⁶ This patient's diet was low in animal protein and consisted primarily of rice and vegetables (he disliked meats, fish, eggs, and dairy products) and plasma Zn level and GH responses to pharmacological stimulation tests were low. After 3 months of oral Zn supplementation, the patient's growth velocity improved

without GH replacement therapy, and the plasma Zn levels and GH responses to stimulation tests normalized.

On the other hand, Siklar et al³⁰ investigated the Zn nutriture of prepubertal GHD patients given GH treatment in Turkey. They measured erythrocyte Zn levels and reported that about one-half of them were Zn deficient. Growth velocity during GH treatment was higher in children with normal erythrocyte Zn levels than those with low erythrocyte Zn concentrations. They also showed that oral Zn supplementation improved the growth velocity of GHD children with Zn deficiency, but not of those without Zn deficiency. These data indicate that Zn status should be evaluated before GH provocative tests and during GH treatment.

MATERNAL ZN NUTRITURE AND PREGNANCY OUTCOME

It has been well known that Zn deficiency during pregnancy may be associated with increased maternal morbidity, prolonged gestation, inefficient labor, atonic uterine bleeding, and increased risks to the fetus.⁴ Maternal Zn deficiency may also cause intrauterine growth retardation (IUGR) and low-birth-weight (LBW) infants.³¹⁻³³ The Zn levels of polymorphonuclear and mononuclear white cells in postpartum women at 24 to 48 hours after delivery were lower in women giving birth to small-for-gestational-age (SGA) infants than those giving birth to appropriate-for-gestational-age (AGA) infants, irrespective of smoking habits.³¹ A significant correlation existed between maternal plasma Zn concentrations measured at mid-pregnancy and an infant's birth weight. The maternal weight at 3 months of gestation and plasma Zn concentrations in the second trimester formed the best predictor model of birth weight.³² It was also reported that the prevalence of LBW infants was significantly higher (8 times) among women with serum Zn concentrations in the lowest quartile in early pregnancy, independent of other

risk factors.³³ However, there have been other studies that showed no association between maternal Zn nutriture and pregnancy outcome.^{34,35} It is also known that plasma Zn concentrations are not reliable indicators of the Zn status and are not useful in estimating marginal Zn deficits.³⁶

The effects of Zn supplementation on pregnancy outcome are not clear.³⁷⁻⁴⁰ The incidence of LBW is very high in many developing countries where Zn deficiencies are prevalent. For example, an estimated 40% to 50% of all live births in Bangladesh were classified as LBW, 70% to 80% of which were the result of IUGR.⁴⁰ Effective interventions aimed at preventing LBW are particularly important to reduce childhood malnutrition and improve infant health. In developing countries maternal Zn supplementation has been suggested as one possible nutritional intervention during pregnancy to improve pregnancy outcomes.⁴¹ Studies of Zn supplementation during pregnancy have been positive and resulted in reduced incidence of IUGR.^{38,39} In a randomized, double-blind, placebo-controlled trial in 580 African-American women, Zn supplementation (25 mg/day) during pregnancy was associated with an increase in birth weight (+126 g) as compared with infants of women who received placebo.³⁹

However, the results of Zn-supplementation trials in pregnant women aimed to improve pregnancy outcome are not consistent.⁴⁰ A double-blind, prospective study carried out in the United Kingdom found no differences in gestational age, birth weight, neonatal abnormalities, and complications of labor and delivery between mothers given a Zn supplement and those given a placebo.³⁷ It is now speculated that Zn supplementation during pregnancy might be beneficial only in populations that are Zn deficient and at high risk for poor fetal growth.⁴⁰

PREVALENCE OF ZN DEFICITS IN HEALTH AND DISEASE STATES

The population groups at risk of Zn deficiency are those who consume low Zn-quality diets. Such diets are rich in phytate and usually contain other ligands that prevent the intestinal absorption of Zn.⁴² On a global scale, protein energy malnutrition is the most common cause of poor growth and short stature, and it appears that Zn deficiency is also prevalent in such populations.⁴ Stunted growth linked to Zn deficiency was found throughout childhood, and depending on the country, 5% to 30% of children were suffering from moderate Zn deficiency, resulting in for small-for-age height.⁴³ However, in recent experimental studies in rats, suboptimal nutrition restricted growth primarily when energy was not ingested in sufficient quantities, whereas suboptimal intake of Zn with an appropriate intake of calories did not stunt growth.⁴⁴

Several studies indicated that marginal Zn deficiency might also be prevalent in infants and children in developed countries. Michaelsen et al⁴⁵ investigated Zn

intake and status in healthy term infants from birth to 12 months of age in Denmark, and found suboptimal Zn status in many subjects during late infancy. They also reported that serum Zn levels at 9 months of age were positively correlated with growth velocity during the period from 6 to 9 months of age. We studied Zn status in short Japanese children with normal GH secretion using the body Zn clearance test to detect marginal Zn deficiency, and found that about 60% of the short children had such a problem. The reason for the high incidence of marginal Zn deficiency in Japanese short children may be due to the recent dietary preference for precooked meals, snacks and convenience foods.⁴⁶

Disorders of the gastrointestinal tract are frequently complicated with Zn deficiency. Breakdown of the integrity of the gastrointestinal tract reduces the normal absorption of dietary Zn and disrupts the enteropancreatic circulation of the ion.¹⁹ There is evidence that patients with Crohn's disease, sprue, or short bowel syndrome may develop Zn deficiency. Several investigators have reported low serum Zn concentrations present in 30% to 70% of patients with Crohn's disease,⁴⁷⁻⁴⁹ and it is not unusual to find depressed urinary Zn excretion.⁵⁰ It has been reported that about 20% to 30% of children with Crohn's disease have severe linear growth retardation, mainly due to malabsorption and malnutrition.⁵¹ On the other hand, it has been reported that about 30% to 70% of children with Crohn's disease have reduced serum Zn levels. Brignola et al⁵² evaluated the effect of oral Zn supplementation on serum Zn levels in patients with Crohn's disease with hypozincemia and concluded that administration of very high doses of Zn (200 mg/day ZnSO₄) for 3 months increased serum Zn levels, but that moderate doses (60 mg/day) did not. We studied Zn status in 30 patients with chronic inflammatory bowel disease (CIBD) and found that 11 subjects had hypozincemia. In addition, those with moderate and severe clinical disease activity had a decreased rise of serum Zn concentration after oral Zn administration. Urinary excretion of Zn after oral load was also remarkably low in all CIBD patients. The abnormalities of Zn metabolism were more frequent among the CIBD patients with growth abnormalities, although they were also found in normal height patients.⁵¹

GROWTH ENHANCEMENT CAPABILITIES OF ZN IN "HEALTHY" INFANTS AND CHILDREN

There have been several reports indicating positive effects of oral Zn supplementation on growth of SGA and/or LBW infants fed artificial formulas.^{45,53,54} In a longitudinal, double-blind, randomized clinical trial in preterm infants in Spain, those fed standard milk formula supplemented with Zn for 6 months had greater linear growth velocity corrected for postnatal age than those without Zn supplementation. Zinc supplementation significantly increased serum and erythrocyte Zn levels and serum ALP activity,⁵³ but no differences were induced in serum IGF-I and IGFBP-3.

IGF-I and IGFBP-3 are of course essential for linear growth in children from childhood to adolescence, but might not be as important for neonates and young infants. There was also a positive effect of Zn supplementation on linear growth in SGA infants fed artificial formula, but not in those fed exclusively breast-milk.⁵⁴ This may be attributed to the lower bioavailability of Zn contained in formula compared to the Zn in human milk, placing formula fed infants at a higher risk of Zn deficiency. Therefore, the effect of Zn supplementation on artificially fed infants would be more evident.⁵³ Mild Zn deficiency in SGA and LBW infants, especially those fed artificial formula, could be a public health problem even in developed countries.

There are several studies that assessed the effects of Zn supplementation on children's growth.^{36,46,55,56} Nakamura et al³⁶ conducted an age-matched control study and showed that oral Zn supplementation was effective in improving the growth rate of short children with marginal Zn deficiency. They also reported that oral Zn supplementation induced increases of serum IGF-I, osteocalcin, and ALP activity.

The effects of oral Zn supplementation were evaluated in short Japanese children with normal GH secretion assessed for Zn status with a body Zn clearance test.⁴⁶ The results indicated that oral Zn supplementation was effective on height gain in short boys with marginal Zn deficiency, but not in girls. There was a significant correlation between the body Zn clearance values and the increase in the growth velocity after oral Zn supplementation in boys, indicating that the degree of Zn deficiency was important. Although the reasons for the difference in the effects of oral Zn supplementation on growth velocity between both sexes are not clear, other studies showed similar differences,⁵⁵ oral Zn supplementation improved growth velocity in boys with idiopathic short stature, but had no effect in girls. On the other hand, a relatively large scale randomized, double-blind, placebo-controlled study showed no positive effect of Zn supplementation on height gain of preschool children.⁵⁶

The results of many other studies are also inconsistent. Brown et al⁵⁷ completed a meta-analysis of randomized controlled intervention trials to assess the effect of Zn supplementation on the physical growth of prepubertal children. After evaluating 33 reports, they found that 26 studies showed positive effects of Zn supplementation on children's linear growth and 7 studies did not. They concluded that interventions to improve children's Zn nutrition should be considered in populations at risk of Zn deficiency, especially where there are high rates of underweight or stunted growth.

ASSESSMENT OF ZN DEFICIENCY AND MARGINAL ZN DEFICIENCY

Unfortunately there is no simple, accurate way, to determine the Zn status of individuals, and this is the

major factor that handicaps the interpretation of the data of most studies and of individual patients. There have been various kinds of laboratory biomarkers proposed to detect definite and/or marginal Zn deficiency. However, these measurements do not accurately reflect nutritionally available Zn pool sizes.¹⁹

Although plasma/serum Zn concentration has been widely used to assess the nutritional status, Zn levels may respond to metabolic conditions unrelated to Zn status and are insensitive to changes in dietary Zn.⁵⁸ The insensitivity of plasma Zn to reductions in dietary Zn intake reflects the tremendous capacity of the organism to conserve tissue Zn by reductions in Zn excretion and/or reductions in the rate of growth. A reduction in plasma Zn concentration does not occur until the capacity to reestablish homeostasis by reducing excretion and/or growth has been exceeded. Plasma Zn represents about 2% of a labile, or nutritionally available, total-body Zn pool that exchanges with isotopic Zn tracers in 24 hours.⁵⁸ Because plasma Zn is the source of this ion for all tissues, plasma concentrations are maintained longer than other components of the body Zn pool.¹⁹

Plasma Zn kinetics or turnover tends to increase with Zn depletion. Thus, the rate of Zn turnover in the plasma compartment or in the total labile pool of the body might indicate the Zn status of an individual. Miller et al⁵⁹ estimated the size of the combined pools of Zn with which plasma Zn exchanged using isotopic Zn. The exchangeable Zn pool size was determined from the amount of isotope introduced into the plasma and the coefficient of the simple exponential decay function fitting enrichment data between day 3 and 9 after isotope administration. They reported that the exchangeable Zn pool size correlated with habitual dietary Zn intake. This excellent assay to detect marginal Zn deficiency may be of little practical use in the clinical situation because of the necessity for isotope administration.

Nakamura et al³⁶ recommended a body Zn clearance test which needs no isotope. This is a kind of a Zn kinetic study; serum Zn levels are measured just before and at 30, 60, 90, 120 minutes after intravenous administration of Zn, the serum Zn decay curve is obtained, and the biological half-life and elimination constant of serum Zn are calculated. The resultant "body Zn clearance" value becomes a sensitive indicator of marginal Zn deficiency.

Other static measurements of Zn status hold little promise. Erythrocyte Zn is mildly affected by Zn deficiency and may not be a sensitive index. The response of leukocyte Zn to changes in Zn status is not consistent among laboratories, and the assay is laborious.¹⁹ Hair Zn levels may be depressed in mild Zn deficiency. However, it is affected by the rate of hair growth and shows seasonal variations.⁶⁰ Urinary excretion rates of Zn are diminished

in severe deficiency states, but this measurement is not sensitive and is confounded by many clinical disorders that increase urinary Zn losses.¹⁹

SUMMARY AND SPECULATION

Zinc, although present in minute quantities in humans, is an essential nutrient and plays an important role as a component of many enzyme systems regulating cell growth, including DNA and protein synthesis, energy metabolism, regulation of gene transcription, hormone levels, and growth factor metabolism.

Nutritional Zn deficiency is still a worldwide public health problem. In developing countries, protein energy malnutrition is the most common cause of poor growth and short stature of children, and Zn deficiency is prevalent in such populations. Zn deficiency in pregnant women is also a serious problem, since it might cause IUGR and LBW infants. Since the incidence of LBW is very high in many developing countries, Zn supplementation in pregnant women should be considered extensively in such regions.

Marginal to moderate Zn deficiency is not uncommon even in developed countries. Zn deficiency should be considered as one of etiologic factors in some children with unexplained short stature. Oral Zn supplementation may be considered as the growth-promoting therapy for children with short stature once marginal Zn deficiency is established. However, the interrelationships among Zn, growth, gonadal function, and GH-IGF-I axis appear to be complex and deserve further investigation.

References

- Thorlacius-Ussing O. *Neuroendocrinology*. 1987;45:233–242.
- Thorlacius-Ussing O, Gregersen M, Hertel N. *Biol Trace Elem Res*. 1988;16:189–202.
- Cunningham B, Mulkerrin M, Wells J. *Science*. 1991;253:545–548.
- Prasad AS. *J Am Coll Nutr*. 1996;15:113–120.
- Ketelslegers JM, Maiter D, Maes M, Underwood LE, Thissen JP. In: Kelnar CJH, et al., ed. *Growth Disorders*. Chapman & Hall: London. 1998;79–96.
- Hubbard SR, Bishop WR, Kirshmeier P, George SJ, Cramer SP, Hendrickson WA. *Science*. 1991;254:1776–1779.
- Vallejo M, Lightman SL. In: Grossman A, ed. *Clinical Endocrinology*, 2nd ed. Blackwell Science Ltd. Oxford. 1998;3–24.
- Nishi Y. *J Am Coll Nutr*. 1996;15:340–344.
- Yamaguchi M. *J Trace Elem Exper Med*. 1998;11:119–135.
- Hall SL, Dimai HP, Farley JR. *Calcif Tissue Int*. 1999;64:163–172.
- Yamaguchi M, Inamoto K. *Metabolism*. 1986;35:1044–1047.
- McDonnell DP, Mongeldorf DJ, Pike JW, Haussler MR, O'Malley BW. *Science*. 1987;235:1214–1217.
- World Health Organization. *Trace Elements in Human Nutrition and Health*. WHO. Geneva. 1996.
- Swanson CA, King JC. *Am J Clin Nutr*. 1987;46:763–771.
- Hambidge KM, Casey CE, Krebs NF. In: Mertz W, ed. *Trace Elements in Human and Animal Nutrition*, Vol 2, 5th ed. Academic Press. New York. 1986;1–137.
- Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended Dietary Allowances*, 10th ed. National Academies Press. Washington, DC. 1989.
- MacDonald LD, Gibson RS, Miles JE. *Acta Paediatr Scand*. 1982;71:785–789.
- Sandstrom B, Cederblad A, Lonnerdal B. *Am J Dis Child*. 1983;137:726–729.
- King JC, Keen CL. In: Shils ME, ed. *Modern Nutrition in Health and Disease*, 9th ed. Lippincott Williams & Wilkins. Philadelphia. 1999;223–239.
- Hunt JR, Gallagher SK, Johnson LK, Lykken GI. *Am J Clin Nutr*. 1995;62:621–632.
- Prasad AS, Miale A, Farid Z, Sandstead HH, Schuler AR. *J Lab Clin Med*. 1963;61:537–549.
- Hambidge KM, Hambidge C, Jacobs M, Baum JD. *Pediatr Res*. 1972;6:868–874.
- Slonim AE, Sadick N, Pugliese M, Meyers-Seifer CH. *J Pediatr*. 1992;121:890–895.
- Aihara K, Nishi Y, Hatano S, et al. *J Pediatr Gastroenterol Nutr*. 1985;4:610–615.
- Miki F, Sakai T, Wariishi M, Kaji M. *Biol Trace Element Res*. 2002;85:127–136.
- Nishi Y, Hatano S, Aihara K, Fujie A, Kihara M. *J Am Coll Nutr*. 1989;8:93–97.
- Oner G, Bhaumick B, Bala RM. *Endocrinology*. 1984;114:1860–1863.
- Ninh NX, Thissen JP, Maiter D, Adam E, Mulumba N, Ketelslegers JM. *J Endocrinol*. 1995;144:449–456.
- Prasad AS, Oberleas D. *J Lab Clin Med*. 1974;83:634–639.
- Siklar Z, Tuna C, Dallar Y, Tanyer G. *J Trop Pediatr*. 2003;49:187–188.
- Simmer K, Thompson RPH. *Clin Sci*. 1985;68:395–399.
- Kirksey A, Wachs TD, Yunis F, et al. *Am J Clin Nutr*. 1994;60:782–792.
- Negggers YH, Cutter GR, Acton RT, et al. *Am J Clin Nutr*. 1990;51:678–684.
- Ghosh A, Fong LYY, Wan CW, Liang ST, Woo JSK, Wong V. *Br J Obstet Gynaecol*. 1985;92:886–891.
- Tamura T, Goldenberg RL, Johnston KE, DuBard M. *Am J Clin Nutr*. 2000;71:109–113.
- Nakamura T, Nishiyama S, Futagoishi-Suginohara Y, Matsuda I, Higashi A. *J Pediatr*. 1993;123:65–69.
- Mahomed K, James DK, Golding J, McCabe R. *Brit Med J*. 1989;299:826–830.
- Simmer K, Lort-Phillips L, James C, Thompson RPH. *Eur J Clin Nutr*. 1991;45:139–144.
- Goldenberg RL, Tamura T, Negggers Y, et al. *JAMA*. 1995;274:463–468.
- Osendarp SJM, van Raaij JMA, Arifeen SE, Wahed MA, Baqui AH, Fuchs GJ. *Am J Clin Nutr*. 2000;71:114–119.
- Gaulfield LE, Zavaleta N, Shankar AH, Meriardi M. *Am J Clin Nutr*. 1998;68(suppl):499S–508S.
- Sandstead HH. *Nutrition*. 1995;11:87–92.
- Favier AE. *Biol Trace Elem Res*. 1992;32:383–398.
- Rising R, Scaglia JF, Cole C, Tverskaya R, Duro D, Lifshitz F. *Nutr Metab*. 2005;2:10.
- Michaelsen KF, Samuelson G, Graham TW, Lonnerdal B. *Acta Paediatr*. 1994;83:1115–1121.
- Kaji M, Gotoh M, Takagi Y, Masuda H, Kimura Y, Uenoyama Y. *J Am Coll Nutr*. 1998;17:388–391.
- McClain C, Soutor C, Zieve L. *Gastroenterology*. 1980;78:272–279.
- Motil KJ, Grand RJ. In: Walker WA, Watkins JB, ed. *Nutrition in Pediatrics*, 2nd ed. B.C. Decker Inc. Publisher. London. 1997;516–533.
- Nishi Y, Lifshitz F, Bayne MA, Daum F, Silverberg M, Aiges H. *Am J Clin Nutr*. 1980;33:2613–2621.
- McClain CJ. *J Am Coll Nutr*. 1985;4:49–64.
- Kanof ME, Lake AM, Bayless TM. *Gastroenterology*. 1988;95:1523–1527.
- Brignola C, Belloli C, De Simone G et al. *Aliment Pharmacol Ther*. 1993;7:275–280.
- Diaz-Gomez NM, Domenech E, Barroso F, Castells S, Cortabarria C, Jimenez A. *Pediatrics*. 2003;111:1002–1009.
- Castillo-Duran C, Rodriguez A, Venegas G, Alvarez P, Icaza G. *J Pediatr*. 1995;127:206–211.
- Castillo-Duran C, Garcia H, Venegas P, et al. *Acta Paediatr*. 1994;83:833–837.
- Kikafunda JK, Walker AF, Allan EF, Tumwine JK. *Am J Clin Nutr*. 1998;68:1261–1266.
- Brown KH, Peerson JM, Rivera J, Allen LH. *Am J Clin Nutr*. 2002;75:1062–1071.
- King JC. *J Nutr*. 1990;120:1474–1479.
- Miller LV, Hambidge KM, Naake VL, Hong Z, Westcott JL, Fennessey PV. *J Nutr*. 1994;124:268–276.
- Gibson RS, Vanderkooy PDS, MacDonald AC, Goldman A, Ryan BA, Berry M. *Am J Clin Nutr*. 1989;49:1266–1273.