Zinc Nutriture in Total Parenteral Nutrition

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Insufficient delivery of zinc during parenteral nutrition leads to declining plasma levels, a negative zinc balance, and occasionally to frank zinc deficiency. Catabolic stress and intestinal fluid losses increase requirements.

Zinc has been recognized as an essential nutrient in humans for over two decades. A secondary or "conditioned" deficiency of zinc first was described in man in 1956.[1] In 1963, zinc deficiency with a *dietary* basis was implicated in the etiology of the syndrome of hypogonadism and dwarfism in rural Middle Eastern communities. Since 1974, the Food and Nutrition Board of the National Academy of Sciences has specified a recommended dietary allowance for zinc; it ranges from 3 mg/day for the infant to 25 mg/day for a lactating woman.[2] Recent surveys suggest that most Americans do not ingest their recommended allowance for zinc.[3] The metallocaloric density of the average American diet does not make it easy to meet the RDA.[4] Since a large portion of the newborn infant's zinc reserves are laid down during the last trimester of pregnancy, prematurity predisposes to precarious zinc nutriture. In addition, periods of rapid growth, such as infancy and adolescence,[5] and pregnancy and lactation increase requirements for zinc.

BIOCHEMICAL AND PHYSIOLOGIC ROLE OF ZINC

Zinc is a vital component of a number of metalloenzymes in mammalian metabolism. Common enzymes, such as carbonic anhydrase, alkaline phosphatase, and carboxypeptidase, are all zinc metalloenzymes. An important feature of zinc metabolism is its role in growth of cells and tissues. This is probably due to its involvement with both the enzymes of nucleic acid metabolism and the translational processes of protein synthesis. Zinc is an important factor in host immune defenses. Zinc deficiency produces impaired granulocyte function[6] and defective cellular immunity.[7,8] Zinc deficiency in man also is associated with impaired taste acuity and dark adaptation.[9,10]

Most TPN fluids deliver a less than sufficient amount of zinc to maintain zinc balance on a 3,000 ml daily infusion.

ZINC DELIVERY DURING TOTAL PARENTERAL NUTRITION (TPN)

The zinc content of fluids used for intravenous alimentation is variable.[11] The range of intrinsic concentration of zinc in a variety of solutions is shown in table 1.[12-18] The concentration of zinc in fluids varied from 0.02 mg to 4.0 mg/liter. Generally, protein hydrolysates have higher zinc concentrations than do the synthetic mixtures of crystalline amino acids in present-day use. When TPN fluids stand for long periods in contact with rubber tubing or stoppers, zinc leaches into solution. Most of the fluids listed in table 1 deliver a less than sufficient amount of zinc to maintain zinc balance on a 3,000 ml daily infusion. Thus, a predictable and adequate delivery of zinc cannot be achieved without supplementation.

MacMahon et al. were probably the first to document a drop in circulating zinc levels in patients receiving parenteral nutrition.[19] Greene et al. subsequently documented a progressive decline in zinc concentration in children undergoing TPN.[13] Two prospective studies published in 1976—one from the Mayo Clinic and the other from the University of Chicago—detailed the dynamics of circulating zinc levels in 18 patients undergoing TPN (figure 1).[20,21] As can be seen, 14 (78%) showed a net decline in zinc concentration during parenteral nutrition, whereas 4 (22%) showed a rise.

Premature infants present a complex problem, since over 60% of the total-body reserves of full-term infants are deposited during the third trimester. A rate of zinc accumulation approaching 500 μg/day is observed in the fetus.[22] As low-birth-weight infants often require parenteral nutrition, this is an important concern. Pichanick et al. observed consistently low serum zinc levels in eight premature babies on TPN for 21 to 23 days with only plasma and blood transfusions as sources of trace elements; no baseline zinc levels were obtained.[23] Michie and Wirth observed serum zinc levels in premature infants (figure 2).[24] Zinc levels were maintained stable for 14 days, but declined when TPN was continued beyond 2 weeks.

Total-Body Zinc Balance

Jacobson and Wester studied zinc balance during TPN in four patients receiving a mean daily intravenous zinc intake of 1,780 μg (range: 1,420 μg to 2,380 μg).[25] Urine, feces, and gastric suction fluid were collected for five days. One patient had a positive daily retention of 710 μg, one was in balance, and two were in negative daily balance of 500 μg and 3,700 μg. In all cases, urinary excretion was the greatest single route of zinc loss.

Wolman et al. studied 24 adult TPN patients for three weeks in seven-day balance periods.[26] The delivery of parenteral zinc was varied in a stepwise fashion in each patient, with dosages of 1.0 mg, 2.5 mg, 4.0 mg, 7.0 mg, 13.0 mg, and 24 mg given daily. The majority of the patients were not acutely ill, but had

Table 1. Zinc and Copper Concentrations of Selected Total Parenteral Alimentation Fluids

Alimentation Preparation	*Commercial Source*	*Zinc (mg/liter)*	*Copper (mg/liter)*	*Country of Origin*	*Reference*
FreAmine	McGaw	0.92–1.62	0.05–0.08	U.S.A.	15
FreAmine	McGaw	0.33–0.42		U.S.A.	21
FreAmine	McGaw	<4.0	0.018	U.S.A.	13
FreAmine II	McGaw	1.34–4.04	0.011–0.009	U.S.A.	18
Amigen	Baxter	1.19	0.020	U.S.A.	18
Amigen	Baxter	2.83–4.01	0.040–0.050	U.S.A.	15
Amigen	Baxter	4.0	†	Israel	14
Aminosol	Abbott	0.03–0.20	0.030–0.050	U.S.A.	15
Polynute	Cutter	2.21–2.90	0.10–0.20	U.S.A.	15
Hyprotigen	†	3.0–3.2	0.023	U.S.A.	16
Casein hydrolysate, 8%	†	<2.1	0.010	U.S.A.	13
VeinAmine	Cutter	0.13–0.15	0.013–0.015	U.S.A.	18
Travamin	Travenol	3.95	0.038	U.S.A.	18
Aminofusin 850	Pfimmer	1.17	0.051	Australia	12
Aminofusin 1000	Pfimmer	0.61	0.044	Australia	12
Aminofusin forte	Pfimmer	0.86	0.137	Australia	12
Ispol, 12%	†	0.08	†	Japan	17
AmiU (essential)	†	0.02	†	Japan	17

Adapted from Ref. 32.
* = not detectable with methods used.
† = datum not available.

inflammatory bowel disease or complications of peptic ulcer surgery with fistulous drainage and/or persistent diarrhea. In 8 patients, none of the three zinc levels administered exceeded total daily zinc losses. In the remaining 16 patients, positive zinc balance was achieved with at least one level of parenteral zinc. In contrast to the findings reported above,[25] zinc lost in gastrointestinal secretions had twice the impact of urinary losses on overall zinc retention.[26] In patients without significant diarrhea or drainage, 2.5 mg to 4.0 mg parenteral zinc maintained positive balance.

The authors observed some interesting and important metabolic consequences of providing adequate zinc infusions to meet losses. For instance, as shown in figure 3, when patients were in positive zinc balance, their nitrogen retention and plasma insulin secretions improved over the corresponding period of negative zinc balance. Thus, providing adequate quantities of zinc appears to favor maximal nutritional recuperation.

In some circumstances, urinary zinc loss can be influenced by factors intrinsic to parenteral alimentation itself. Freeman et al. noted that autoclaving amino acid mixtures with dextrose caused a three- to fourfold increase in urinary zinc excretion, presumably due to the formation of a potent chelating compound that complexed endogenous zinc and provoked its excretion by the kidneys.[27] Similarly, high levels of free amino acids with concomitant aminoaciduria can produce excessive zinc excretion.[28,29] It appears that some amino acids, such as histidine, have a

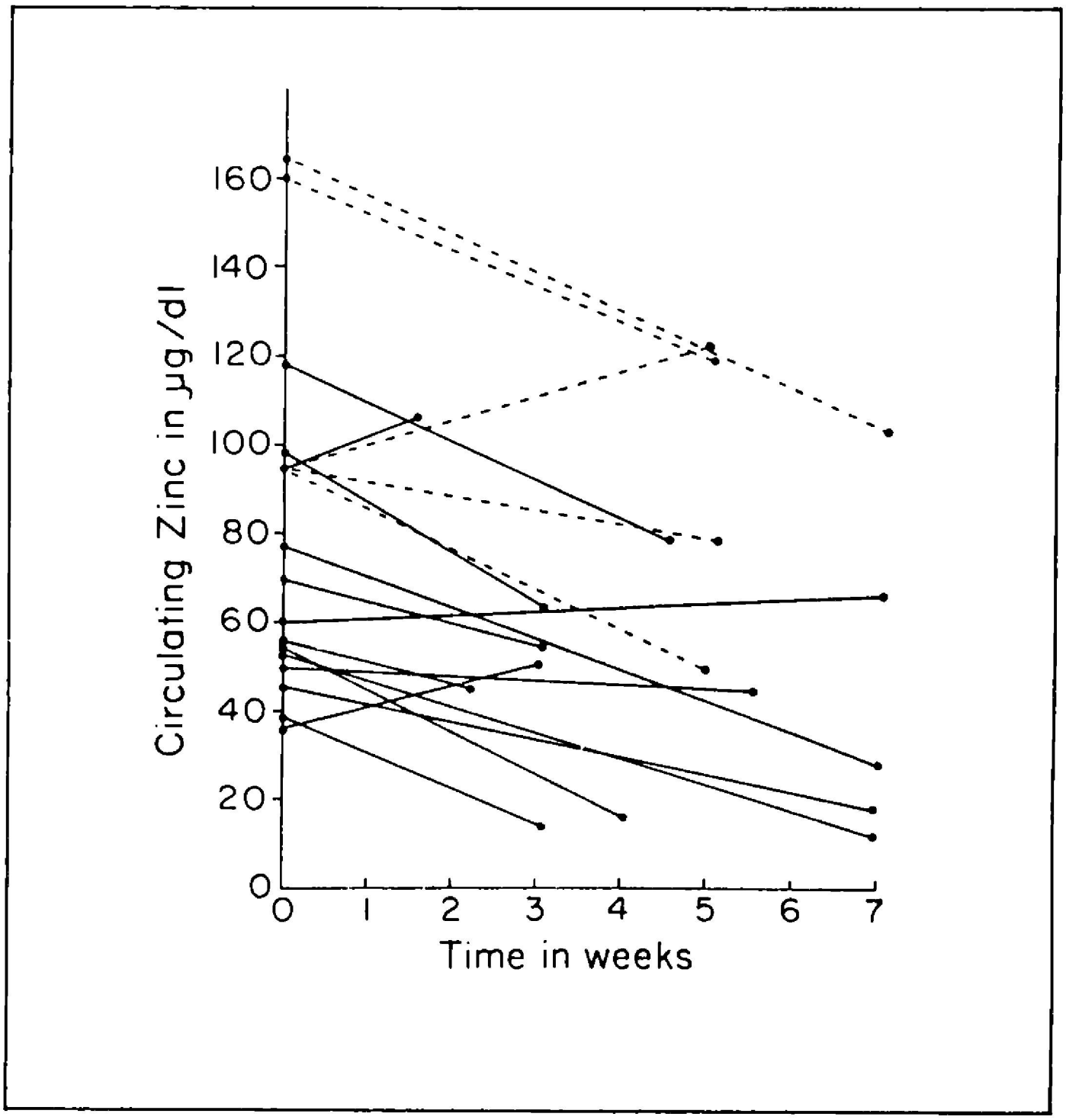

Figure 1. The net change in circulating zinc concentrations during total parenteral nutrition of 18 patients (from two reported series), followed from initiation to termination of treatment. The dotted lines represent 5 patients from the Mayo Clinic;[20] the solid lines represent 13 patients from the University of Chicago.[21] Reproduced by permission from Ref. 11.

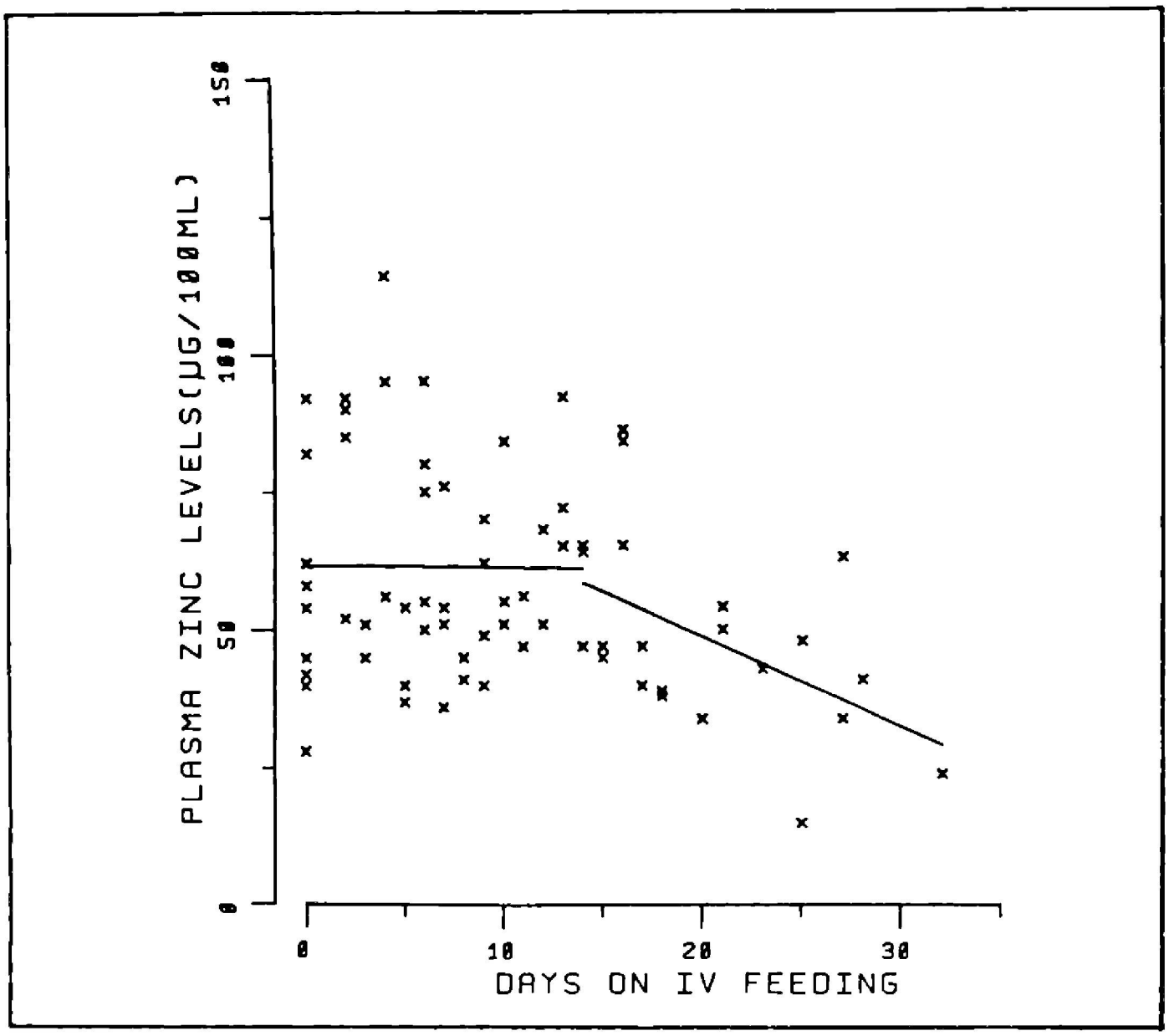

Figure 2. Plasma zinc concentrations of 9 premature infants during parenteral nutrition. During the first 14 days of parenteral nutrition there was no statistically significant change in plasma zinc values; from day 14 to day 32 there was a progressive decline. Linear regression analysis demonstrated that the slope of this line was significantly different from zero ($P<0.05$). Reproduced by permission from Ref. 24.

greater potential to promote hyperzincuria than others.[30,31]

Zinc Deficiency

In addition to depressed circulating levels and negative zinc balance, overt clinical zinc deficiency occurs during TPN. The first well-documented cases were reported by Kay and Tasman-Jones.[32] Apathy, mental depression, alopecia, perioral eczematoid skin lesions, and diarrhea characterized postsurgical patients with severe gastrointestinal diseases receiving TPN.[32-34] Their daily urinary zinc output ranged from 4 mg to 20 mg. All of the adverse symptoms disappeared with zinc supplementation. Since then, many authors have observed or commented on clinical aspects of TPN-associated zinc deficiency.[13,17,20,34-52]

Skin lesions and alopecia have been the hallmark signs reported.[32-40,44-49,52] The cutaneous manifestations of zinc deficiency often bear a clinical and histologic resemblance to acrodermatitis enteropathica, an inborn error of zinc metabolism. It is important to realize that not all nutritional skin rashes that occur during TPN are related to zinc deficiency; essential fatty acid deficiency[39] and biotin deficiency[54] also can produce

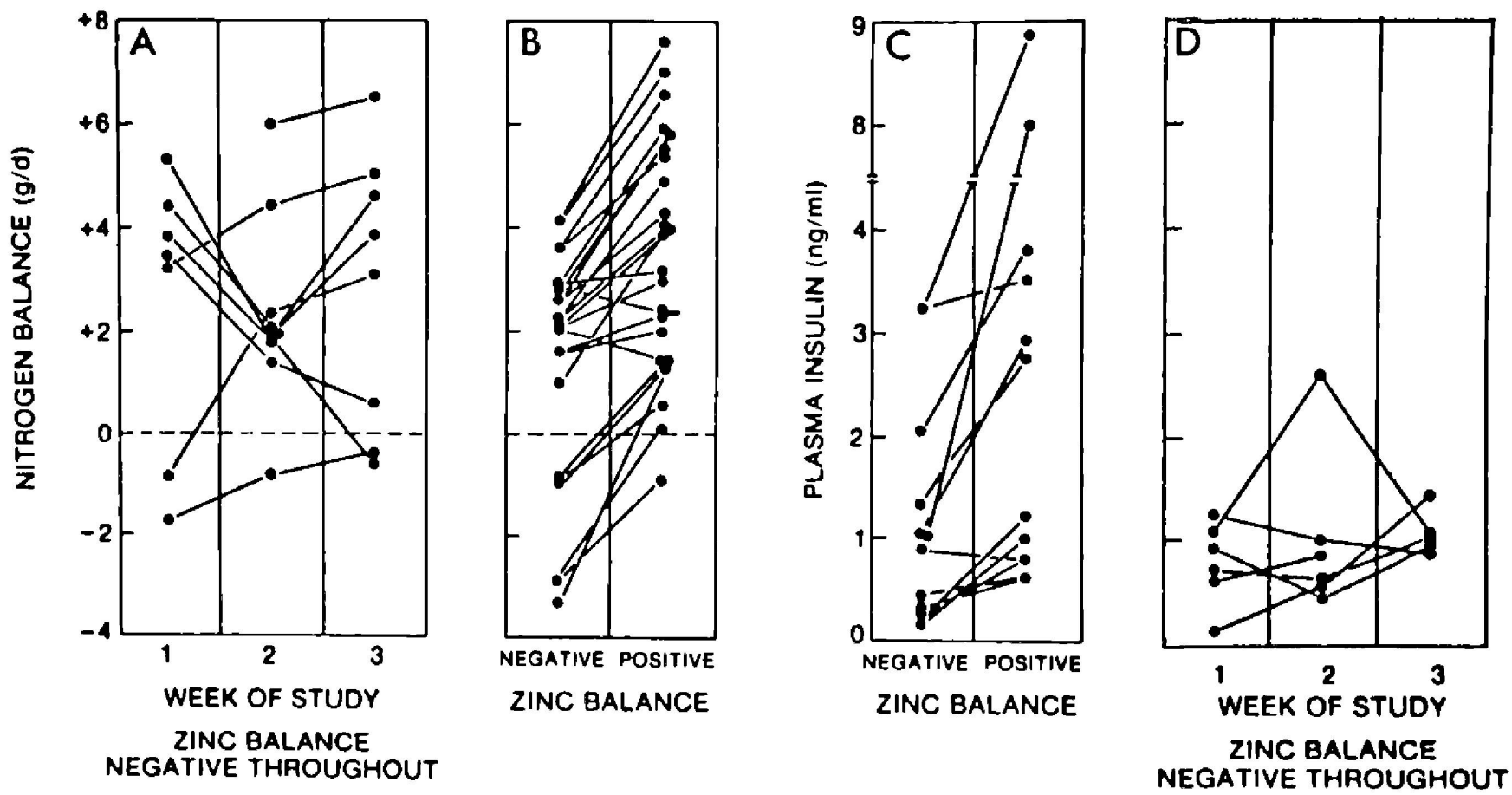

Figure 3. Relation of zinc balance to nitrogen balance (A and B) and to plasma insulin (C and D). A, nitrogen balance, over successive weeks of study, in 8 patients who were in negative zinc balance continuously. B, Nitrogen balance when given a patient, in two different weeks, was in negative and positive zinc balance, respectively. C, Plasma insulin when given a patient, in two different weeks, was in negative and positive zinc balance, respectively. D, Plasma insulin when a given patient was in negative zinc balance throughout the three weeks of study. Reproduced by permission from Ref. 26.

skin lesions in parenteral alimentation patients. Immune defects—primarily of cell-mediated immunity—have been observed in patients depleted of zinc during TPN.[43,50]

Signs of zinc deficiency occur in pediatric patients as well as in adults.[35,37,43,44,50,52]

Assessing Zinc Status

Medical professionals caring for patients on TPN should remain alert to signs of potential zinc deficiency. The laboratory monitoring of zinc nutriture in patients on TPN presents problems, since there is no unequivocal laboratory index that reflects total-body zinc nutriture.[55]

The most accessible laboratory parameter of zinc status is the circulating (serum or plasma) zinc concentration. If a baseline determination at the onset of TPN is available, the change in concentration, measured serially, usually reflects changes in nutritional status. However, infections and low albumin concentrations can depress zinc levels even when stores are adequate. Thus, an isolated low zinc value itself is not a definitive indicator of zinc deficiency.

Conversely, a normal zinc level is no assurance of zinc adequacy. Strobel et al. found zinc-responsive cutaneous changes in three individuals whose serum zinc levels were normal or elevated.[47] Premature infants are susceptible to zinc depletion;[56] however, circulating zinc levels of 134 μg/dl ± 37 (mean ± SD) and 110 μg/dl ± 28 at birth were found in two groups of premature children less than 28 weeks and between 28 and 31 weeks, respectively.[56] The standard criteria for adequate plasma zinc levels in the premature infant may not be applicable. A significant degree of zinc depletion may exist in these infants despite zinc levels in the apparently "normal" range.

Circulating levels of alkaline phosphatase, a zinc metalloenzyme, also reflect zinc status during TPN.[35,37,47,48,52,53] In three patients with clinical manifestations of zinc deficiency reported by Strobel et al., alkaline phosphatase levels had fallen from initial levels by an average of 60% during the dermatitis phase.[47] In a South African hospital in which zinc determinations were not available, the response of alkaline phosphatase to zinc administration was used as an ancillary guide in diagnosis and management of a patient who developed acrodermatitis-like lesions during TPN.[48] Kasarskis and Schuma have reviewed much of the published literature on zinc deficiency and alkaline phosphatase change in patients undergoing TPN.[53] They found a significant linear relation between the serum or plasma zinc level at the time that zinc therapy was initiated and the absolute change in alkaline phosphatase from onset to recovery. Alkaline phosphatase level is not an infallible indicator, especially in premature and young infants. Bone development, calcium intake, and vitamin D status proved to be much more potent determinants of circulating alkaline phosphatase activity than zinc status among premature infants followed prospectively in a neonatal intensive care facility.[56]

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RECOMMENDATIONS FOR ZINC SUPPLEMENTATION

Wretlind was probably the first to advocate the supplementation of total parenteral nutrition regimens with zinc, suggesting that 1.4 mg zinc be provided to adults daily.[57] Shils recommended 2 mg zinc daily during TPN.[58]

In 1979, the American Medical Association recommended that *individual* trace element solutions be formulated for addition to parenteral mixtures; an appropriate ionic concentration for zinc is 1 mg/ml sterile, pyrogen-free stock solution.[59]

The suggested daily intravenous dosages of zinc defined by the AMA committee are shown in table 2. Catabolic stress—fever, infection, surgery, trauma—increases the parenteral requirement by an average of 2 mg zinc daily. Taking into account the observations of Wolman et al.,[26] the committee noted that loss of intestinal fluid results in a larger replacement requirement for parenteral zinc. This is especially important when TPN is used for "bowel rest" in patients with fistulous inflammatory bowel disease.

The experience of Latimer et al. illustrates the care that must be exercised in formulating nutritional regimens for TPN.[52] They reported two infants with severe short-bowel syndrome in whom parenteral feeding was continued while attempts were made at sustaining oral intake. The infants received 40 μg to 50 μg/kg/day zinc (half the AMA recommendation). A progressive fall in serum zinc levels and negative zinc balance produced a rash consistent with zinc deficiency. A fourfold increment in zinc dose was required to maintain balance, restore circulating levels, and resolve the cutaneous manifestations.

Zinc Preparations for Intravenous Administration

Before the U.S. Food and Drug Administration licensed commercial zinc preparations for intravenous use, special sterile, pyrogen-free solutions had to be prepared individually in hospital pharmacies. An up-to-date (but not exhaustive) list of commercial zinc preparations for parenteral administration is shown in table 3. Both single-entity and multiple-element preparations are available. The AMA committee cautions against using the multielement preparations because they "present a risk of overdosage when the need for one trace element is appreciably higher than that for the other trace elements present in the formulation."[59] For routine replacement in the stable adult patient, the multielement formulations are convenient; but when specific manipulation of zinc dosage is required, all *additional* zinc must come from a single-entity (zinc) solution.

Toxicity of Parenteral Zinc

There have been very few reports of toxicity from administering excessive

Table 2. Suggested Daily Intravenous Zinc Intake

Patient Group	Dosage
Premature infants weighing 1.5 kg to 3.0 kg	300 μg/kg
Full-term infants through children up to 5 years	100 μg/kg
Stable individuals over 5 years of age	2.5 mg to 4.0 mg
Acute catabolic states in individuals over 5 years	4.5 mg to 6.0 mg
Stable adults with intestinal fluid losses	12.1 mg/liter small-bowel fluid lost and 17.1 mg/kg of stool or ileostomy output

Source: Based on American Medical Association: Guidelines for Essential Trace Element Preparation for Parenteral Use.[39]

Table 3. Selected Commercial Zinc Preparations for Parenteral Administration[a]

Preparation	Zinc Form	Mineral, Dosage	Delivery Form	Source
Sterile zinc chloride	zinc chloride	zinc, 1 mg/ml	10 ml vial	Abbott Laboratories, North Chicago, IL
Sterile zinc sulfate	zinc sulfate	zinc, 4 mg/ml	10 ml vial	International Medications Systems Limited, S. El Monte, CA
Multiple Trace Metal Additive	zinc sulfate	zinc, 4 mg/ml copper, 1 mg/ml manganese, 0.5 mg/ml chromium, 10 μg/ml	1 ml vial 5 ml vial 10 ml vial	
NEDH Formulation	zinc sulfate	zinc, 1.5 mg/ml copper, 0.5 mg/ml manganese, 0.2 mg/ml iodine, 28 μg/ml chromium, 5 μg/ml	10 ml vial	Pentcal, Allston, MA
Sterile zinc sulfate	zinc sulfate	zinc, 5 mg/ml	5 ml vial 10 ml vial 30 ml vial	Lypho-Med, Chicago, IL
M.E.T.-4 (Mixture of Trace Element Additives)	zinc sulfate	zinc, 1 mg/ml copper, 0.4 mg/ml manganese, 0.1 mg/ml chromium, 4 μg/ml	10 ml vial	

[a] This is not an exhaustive listing of all of the formulations of zinc commercially available at the time of publication. Mention of a trademark or proprietary product does not constitute an endorsement nor a guarantee or warranty of the product, and does not imply its approval to the exclusion of other products that may be suitable.

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parenteral zinc. Bos et al. reported that a rapid infusion of parenteral fluid (containing 9.8 mg zinc per liter) produced transient flushing, blurred vision, and sweating.[41] In a Brazilian hospital, a 10-fold error in the formulation of parenteral mixtures was made in which 23 mg (instead of 2.3 mg) zinc were added to the infusates. A retrospective survey of patients who received these solutions revealed an asymptomatic hyperamylasemia (without clinical pancreatitis) in seven patients.[60]

Brooks et al. reported the death of a home dialysis patient resulting from the inadvertent infusion of 1.6 g zinc intravenously during a two and one-half day period.[61] The presenting manifestations were hypotension, pulmonary edema, vomiting, diarrhea, jaundice, and oliguria. Serum zinc concentration rose to 4,184 μg dl, 40 times the normal level. Hyperamylasemia without pancreatitic signs, a cholestatic liver chemistry profile, and an acute anemia and thrombocytopenia developed. The patient died of uremic and septic complications 47 days after the incident. Thus, the possible adverse reactions, from mild to massive parenteral overdosage with zinc, mandate extreme caution in the prescription, formulation, and administration of supplemental zinc during TPN.

ZINC DEFICIENCY IN ENTERAL NUTRITION

Zinc deficiency due to poor composition of the formula is a potential hazard not only in TPN, but also in enteral alimentation. Pekarek et al. reported a decerebrate patient in a rehabilitation hospital who had been tube-fed, for an unspecified time, commercial vitamin-enriched formula (Compleat-B).[62] The patient apparently developed zinc depletion, suggested by seborrheic skin lesions, a nonhealing decubitus ulcer, cutaneous anergy, impaired T-cell function in vitro, and a low plasma zinc level. Analysis of the formula solution showed a zinc content of 7.6 mg/liter. The entire constellation of zinc deficiency manifestations resolved with the oral administration of 22.7 mg zinc daily.

Circulating levels of alkaline phosphatase, a zinc metalloenzyme, also reflect zinc status during TPN.

CONCLUSIONS

As zinc is an essential nutrient, it must be provided in the diet, whether that diet is oral or intravenous. Insufficient delivery of zinc during parenteral nutrition leads to declining circulating concentrations, a negative zinc balance, and occasionally to signs of frank zinc depletion. Catabolic stress and intestinal fluid losses increase the parenteral requirements for zinc. During TPN, nutritional repletion may be enhanced by maintaining a positive zinc balance, as nitrogen retention and insulin secretion are enhanced under these conditions. Sterile, pyrogen-free zinc preparations for parenteral administration recently have become available commercially. Attention to providing adequate zinc nutrition during TPN is the obligation of all professionals managing parenterally alimented patients.

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