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Zinc: Physiology, Deficiency, and Parenteral Nutrition

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Abstract

The essential trace element zinc (Zn) has a large number of physiologic roles, in particular being required for growth and functioning of the immune system. Adaptive mechanisms enable the body to maintain normal total body Zn status over a wide range of intakes, but deficiency can occur because of reduced absorption or increased gastrointestinal losses. Deficiency impairs physiologic processes, leading to clinical consequences that include failure to thrive, skin rash, and impaired wound healing. Mild deficiency that is not clinically overt may still cause nonspecific consequences, such as susceptibility to infection and poor growth. The plasma Zn concentration has poor sensitivity and specificity as a test of deficiency. Consequently, diagnosis of deficiency requires a combination of clinical assessment and biochemical tests. Patients receiving parenteral nutrition (PN) are susceptible to Zn deficiency and its consequences. Nutrition support teams should have a strategy for assessing Zn status and optimizing this by appropriate supplementation. Nutrition guidelines recommend generous Zn provision from the start of PN. This review covers the physiology of Zn, the consequences of its deficiency, and the assessment of its status, before discussing its role in PN. (*Nutr Clin Pract*. XXXX;xx:xx-xx)

Keywords

deficiency; total parenteral nutrition; zinc; nutrition

Zinc (Zn) is a dietary micronutrient, known since 1961 to be essential for human physiology.[1] The focus of this article is to provide an overview of Zn in the context of parenteral nutrition (PN). However, it is first necessary to understand the biology of Zn and how to assess its status. The review therefore starts by covering the relevant physiology, Zn deficiency, and biomarkers of Zn status and then goes on to cover Zn's role in PN.

Physiology

Zn is the second-most abundant trace element in the body (after iron) and the most abundant intracellular one. The total body complement in an adult is about 2 g, >95% of which is intracellular. It is ubiquitously present in all tissues and body fluids but predominantly located in skeletal muscle and bone. Although Zn is abundant in the body, there is no dedicated store. Tissue turnover makes it available for use elsewhere in the body, but this is a slow process. A small functional pool accounts for about 10% of intracellular Zn in liver and other tissues.[2] It exchanges with the plasma pool (0.1% of total body Zn), the turnover of which is rapid. In plasma, most Zn is bound to albumin and alpha 2 macroglobulin. The plasma concentration is maintained by conservation and redistribution. It is subject to a diurnal rhythm, being highest at 10 AM.[3] It also has high biological variation, with an intraindividual coefficient of variation of 11%.[4]

The physiologic roles of Zn can be divided into catalytic, structural, and regulatory. There are about 300 Zn metalloenzymes, including carbonic anhydrase, alkaline phosphatase, alcohol dehydrogenase, DNA polymerase, protein chain elongation factor, and copper (Cu)–Zn superoxide dysmutase.[5,6] Zn is an integral component of these enzymes, rather than a positive regulator. Collectively, these enzymes are required for metabolism of carbohydrate, fat, and protein and clearance of reactive oxygen species. Zn has a role in vision—both in vitamin A transport as a component of retinol binding protein (RBP) and in rhodopsin synthesis.[7] The structural roles are in proteins, cell membranes, nucleic acids, and ribosomes. It has regulatory roles in gene transcription, cell signaling, hormone release, and apoptosis.[8] About 3000 transcription factors contain Zn.[5]

The requirement of numerous proteins for Zn makes it is essential for the normal functioning of anabolic processes, such as growth, tissue maintenance, and wound healing. For growth to proceed, there must be, in addition, a sufficient macronutrient supply. The nutritional content of the diet is linked to growth by the action of the peptide hormone insulin-like growth factor I (IGF-I). IGF-I stimulates cellular proliferation and uptake of amino acids and glucose, which are required by proliferating cells.[9] The presence of normal plasma concentrations

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of IGF-I signals the availability of sufficient nutrients for growth to proceed. Adequate Zn status is necessary for the maintenance of plasma IGF-I concentrations even when energy intake is adequate. This makes sense physiologically because Zn is an indispensable component of growing tissues.

Absorption and Excretion

Zn is absorbed in the duodenum and proximal jejunum, being transported into enterocytes by specific transporters expressed in the apical membrane.[10] Absorption is enhanced by citric acid and inhibited by iron, fiber, and phytate, which is a chelator of Zn.[11,12] The bioavailable fraction is the proportion retained and used by the body. It is high in diets rich in meat and low in vegetarian diets because of their phytate content. Strict vegetarians may require 50% more Zn in their diet. Absorbed Zn is either transported to the liver through the portal system or bound to metallothionein (MT) intracellularly in enterocytes. The MT bound fraction is later returned to the bowel during shedding of enterocytes. Zn is efficiently excreted into bile at a concentration of around 4 µg/mL.[13] Some of the secreted Zn is reabsorbed, undergoing an enterohepatic circulation, the net gastrointestinal (GI) loss being 2–4 mg/d. Urinary Zn excretion in adults is about 0.5 mg/d. Other physiologic losses occur in skin and hair.

Homeostasis

Homeostasis maintains a constant intracellular Zn concentration and a plasma concentration within the reference range of 11–25 µmol/L (0.7–1.6 mg/L).[3] Homeostatic regulation occurs at the levels of intestinal absorption, GI excretion, urinary excretion, and cellular retention, the most important target of regulation being net intestinal absorption.[14] When the dietary Zn content decreases, fecal losses decrease, enabling the efficiency of absorption to increase to almost 100%.[15] There is also decreased urinary Zn excretion[15,16] and increased cellular retention.[17] Tissue Zn is conserved by reduction in growth caused by low-circulating IGF-I. However, adaptive mechanisms cannot eliminate losses altogether. Consequently, a dietary supply of Zn remains essential even during adaptation. Depletion studies observed a 65% decrease in plasma Zn caused by a decrease in the rate constant for release from the most slowly turning-over pool.[15] This pool is probably located in skeletal muscle and appears to be sensitive to intake.

When dietary Zn increases, excess is chelated by MT in enterocytes, preventing its access to the systemic circulation and causing it to be returned to the lumen once the enterocytes are shed. Liver MT also chelates excess Zn, and urinary excretion increases.[18] These adaptive mechanisms enable balance to be maintained over intakes ranging 22–306 µmol/d.[16] Zn homeostasis is outlined in Figure 1.

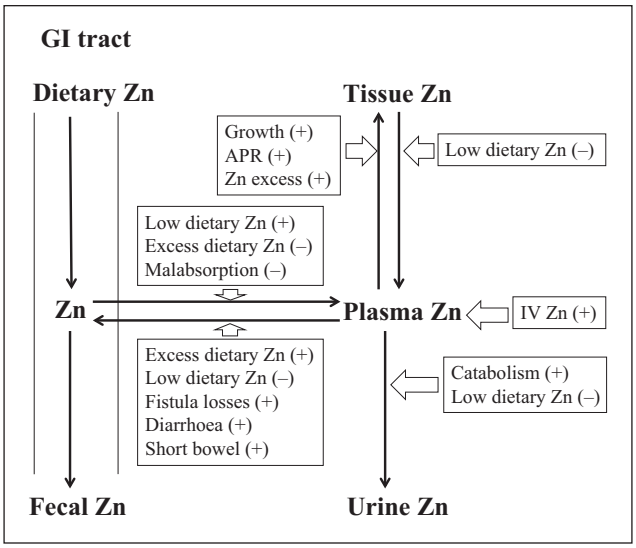

Figure 1. Zn homeostasis. Dietary Zn is absorbed in the upper GI tract into enterocytes. Some is chelated into the enterocyte and physiologically returned to the GI tract upon mucosal shedding. Absorbed Zn enters a small, rapidly turning-over plasma pool, from which it is redistributed to tissues in which the majority of body Zn is located. Zn balance is maintained principally by regulation of net GI absorption. Adaptive mechanisms maintain normal Zn status in the face of decreases or increases in dietary Zn. Adaptive, pathologic, and therapeutic influences on Zn distribution are shown: +, positive influence; –, negative influence. APR, acute phase response; GI, gastrointestinal; IV, intravenous; Zn, zinc.

Requirements in Health

Optimal oral requirements for health have been difficult to determine because of differences in bioavailability among diets and a lack of reliable markers of Zn status. The UK reference nutrient intake (RNI) for Zn is 9.5 mg/d (145 µmol/d) in adult males and 7.0 mg/d (110 µmol/d) in adult females.[19] Only 2.5% of the population requires more than this. In the United States, dietary reference intakes (DRIs) have been compiled by the Institute of Medicine[20] based on metabolic balance studies. The recommended dietary allowance (RDA) is 8–11 mg/d, which meets the nutrient needs of 98% of the population. Physiologic requirements peak at puberty coincident with rapid bone growth. Infants, children, pregnant and lactating women, and the elderly also have increased requirements. To avoid toxicity, the US Food and Drug Administration set the tolerable upper limit for adults of Zn at 40 mg/d.[21] These recommendations apply to enteral intake in stable patients.

Zn Deficiency

The absence of a dedicated store has the consequence that there is impairment of function when Zn status is compromised. When Zn intake decreases, homeostatic mechanisms initially maintain the plasma concentration within the reference range; but when deficiency is severe, the concentration decreases, and

Table 1. Causes of Zinc Deficiency.

Class of Causes	Individual Causes
Inadequate intake	*GI disease*: Crohn's disease, jejunoileal bypass, previous bariatric surgery, small bowel resection, acrodermatitis enteropathica *Pancreatic disease*: alcoholic pancreatitis, cystic fibrosis
Reduced absorption	Low dietary zinc, inadequately supplemented nutrition, diet rich in phytate, sodium polyphosphate or EDTA
Increased losses	*GI*: inflammatory bowel disease, diarrhea, steatorrhea, enterostomy, fistula, chyle leaks *Skin*: burns *Urine*: burns, trauma, sepsis, renal disease, alcoholism, drugs (eg, thiazides, penicillamine, diethylenetriamine pentacetate, valproate, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, EDTA-containing propofol and chelating agents, cysteine, cisplatin) *Dialysate*: hemofiltration
Increased demand	Systemic illness resulting in increased oxidative stress

this is followed by clinical symptoms, the severity of which increase with the degree of deficiency. Zn deficiency varies in severity from mild, in which there are nonspecific clinical consequences, to severe, characterized by overt clinical features.

Causes of Zn Deficiency

Zn deficiency can occur as a result of inadequate intake, reduced absorption, increased losses, or increased demand. The commonest worldwide cause is inadequate intake as a result of a diet low in Zn or rich in phytate. The population groups most at risk of developing Zn deficiency are those with the greatest physiologic requirements. It is most prevalent in South Asia in pregnant and lactating women.[22] The elderly are at risk because of poor diet and age-related decline in absorption. The ZENITH European population study reported a 5% prevalence of Zn deficiency in healthy free-living elderly subjects.[23] A prevalence of 28% has been reported in hospitalized elderly subjects.[24] Prevalence in children is increasing in the developed world.[25] It has recently been reported that children on overly restrictive diets because of suspected food allergy are at risk of deficiency.[26]

Dietary deficiency is particularly likely in patients with anorexia nervosa or alcohol dependence. Intake may be insufficient in patients receiving nutrition support that is inadequately supplemented. Patients with GI disease are at risk because of reduced absorption or increased losses. Fistula fluid is rich in Zn metalloproteins, the losses of which are higher when the fistula is more distally located in the GI tract. Acrodermatitis enteropathica is a recessively inherited condition that results in a failure of Zn absorption. It is associated with a characteristic severe skin rash and is fatal if untreated. Although acrodermatitis enteropathica is rare, its study has advanced understanding of Zn deficiency. Patients with sustained bile losses would be expected to lose significant amounts of Zn.[13] Assuming that 500 mL of bile is produced per day, around 2 mg of Zn will be lost by this route, an amount comparable to the standard daily provision in PN. Patients with chyle leaks would also be expected to suffer significant Zn losses because chyle is protein rich. However, there is no published information on the Zn content of chyle. Burns result in substantial cutaneous losses.[27]

Increased urinary losses can occur in conditions associated with muscle catabolism, such as sepsis, or iatrogenically from prolonged use of drugs, including thiazide diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Patients on long-term treatment with these drugs are therefore vulnerable to Zn deficiency. Patients treated by hemofiltration are often Zn deficient possibly because of dialysate losses.[28] However, no Zn is lost during peritoneal dialysis.[29] The oxidative stress accompanying systemic illness can contribute to micronutrient deficiency by increasing the demand for antioxidants, including Zn, selenium, and vitamins A, C, and E.[30]

It is well recognized that patients requiring bariatric surgery are at risk of Zn and other micronutrient deficiencies both pre- and postoperatively.[31,32] Patients who have had biliopancreatic diversion surgery are at greatest risk, with up to 92% reported to be deficient 1 year postoperatively.[33] This was illustrated by a recent case report in which a patient having biliopancreatic diversion surgery presented postoperatively with a wound infection and rash caused by severe Zn deficiency.[34] To prevent deficiency arising postoperatively, it is advisable to test Zn status preoperatively and to correct it, if necessary.[35] Postoperatively, patients require daily multi–trace element and multivitamin supplements. It has been recommended that patients take the RDA plus an additional 300% post–biliopancreatic diversion surgery and the RDA plus an additional 30% post–gastric bypass surgery. Elsewhere, it has been recommended that patients having bariatric surgery should take an additional 6.5 mg of Zn daily.[36] Supplementation should be given orally where possible. Guidelines also recommend regular monitoring of micronutrient status post–bariatric surgery.[37] The causes of Zn deficiency are listed in Table 1.

Acute Phase Response

During the acute phase response (APR), there is hypozincemia caused by a redistribution of Zn from the vascular compartment into cells. There is a cytokine-mediated increase in vascular permeability causing albumin to move from the vascular to extravascular compartment carrying bound Zn.[38,39] Cytokines also increase MT synthesis, resulting in Zn sequestration in enterocytes and hepatocytes.[12,40,41] The biological purpose of this redistribution is uncertain, but it may help prevent bacterial invasion by depriving circulating microorganisms of Zn.[42] It may also help to meet the requirement for neutralization of reactive oxygen species and synthesis of acute-phase proteins such as C-reactive protein (CRP). Hypozincemia occurring during the APR therefore does not necessarily imply that there is deficiency. Indeed, overzealous supplementation in this situation may result in Zn excess. A recent study of critically ill patients showed that while plasma Zn concentrations decreased, erythrocyte Zn concentrations were normal, suggesting adequate nutrition status over the previous 2 months.[43] However, acute illness can precipitate overt deficiency in patients with preexisting mild deficiency. It may do this in part by exacerbation of urinary Zn losses.[44]

Observations that the plasma Zn concentration decreases in relation to the severity of inflammation has prompted authors to investigate the prognostic value of its measurement. In critically ill patients, it has been reported to correlate negatively with the degree of organ failure and concentration of the cytokine IL-6.[45] Plasma Zn is lower in patients with certain cancers in which it has been used as an index of disease extent.[46,47] Another condition associated with increased cytokine concentrations is obesity. Obese individuals with low dietary Zn intake have upregulated IL-1 alpha and IL-6 and lower Zn concentrations intracellularly and in plasma.[48] Zn deficiency appears to upregulate cytokines. As such, it may have a role in the development of cardiovascular disease.[49]

Consequences of Zn Deficiency

Deficiency can compromise any process in which Zn metalloproteins participate. As might be expected from the large number of these processes, the consequences of deficiency are diverse. Their severity depends on the severity and duration of deficiency and the age and sex of the patient. The patient may report symptoms such as anorexia and loss of taste sensation (dysgeusia) and altered smell sensation (dysosmia). Diarrhea can occur, increasing Zn losses and resulting in a vicious cycle of worsening deficiency. A skin rash can occur in severe deficiency.[50] There may be decreased vitamin A release from the liver, contributing to night blindness.[7] Handling of reactive oxygen species may be impaired, rendering cells susceptible to oxidative damage to DNA and to the cell membrane.[6] The immune system may be compromised, promoting the development of infection (eg, pneumonia in patients who have sustained burns).[51] In these patients, Zn replacement was associated with decreased pneumonia and shorter hospital stay. Zn deficiency can also cause gonadal hypofunction, decreasing plasma testosterone concentrations and fertility.[50]

Because Zn is indispensable for growth and tissue maintenance, its deficiency may present as growth failure, alopecia, and a decline in muscle work capacity.[52] There may be delayed attainment of positive nitrogen balance during recovery from illness or surgery. These effects of Zn deficiency are caused by its suppression of IGF-I and reduction in gene transcription.[53] The decrease in plasma IGF-I is independent of energy intake and resistant to exogenous growth hormone.[54] Growth impairment is compounded by the anorectic effect of Zn deficiency, which decreases substrate availability by reducing food intake. Growth failure does not respond to restoration of energy and amino acid supply until Zn status has been corrected. Deficiency during pregnancy has diverse effects on the fetus, including prematurity, complicated delivery, low birth weight, and congenital abnormality.[55] There may be adverse effects on fetal brain function, including impaired cognitive development.[56,57] There is evidence from experimental work that implicates Zn deficiency in the development of anastomotic leaks.[58]

Refeeding syndrome is a disorder in which clinical consequences follow the provision of macronutrient to a malnourished patient.[59] It is associated with fluid shifts and electrolyte abnormalities, which can be life threatening if untreated. During refeeding, the reintroduction of macronutrients results in increased substrate availability. However, the function of the enzymes that metabolize this substrate may be impaired because of cofactor deficiency. This results in impaired energy generation. If the demand for micronutrients is not met, then deficiency may present acutely. Vitamin B_1 (thiamine) deficiency is an important component of refeeding syndrome, but deficiencies of other micronutrients also occur and should be considered as part of refeeding syndrome.[60] There is increased demand for Zn, particularly once the patient becomes anabolic. This can cause deficiency to manifest itself. For example, skin rash has been reported to coincide with the period of rapid growth in preterm infants.[44] When nutrition support is commenced, sufficient micronutrients should be provided to enable effective metabolism of substrates. Guidelines on preventing refeeding complications have recommended generous provision of B vitamins in the early stages of refeeding. However, other micronutrients, including Zn, should be considered. This is discussed further below in the section on supplementation of Zn in patients receiving PN.

Hepatic encephalopathy is a complication of liver cirrhosis characterized by a reversible decline in cognitive function. Ammonia is thought to be a key pathologic factor. There is interest in Zn as a potential treatment, in part because it is required for detoxification of ammonia by participating in its enzymatic conversion to urea in liver and to glutamine in both muscle and astrocytes.[61,62] Zn deficiency is also well recognized to be

Table 2. Consequences of Zinc Deficiency.

System	Consequences
Epidermal	Skin rash, alopecia, nonhealing ulcers, delayed wound healing
Gastrointestinal	Dysgeusia, diarrhea
Central nervous	Impaired cognitive function, dysosmia
Immune	Recurrent infections
Skeletal	Poor growth
Reproductive	Hypogonadism, low birth weight, congenital abnormality

common in patients with hepatic encephalopathy.[63] A recent study compared serum trace element levels in patients with compensated versus decompensated liver cirrhosis. Zn levels were lower in the decompensated group.[64] In a placebo-controlled trial of Zn treatment of patients with liver cirrhosis, hyperammonemia, and hypozincemia, a significant reduction in ammonia levels was observed in the treatment group.[65] One notable case report described a patient whose encephalopathic symptoms responded to oral Zn treatment and recurred during Zn deficiency.[66] The encephalopathy improved in response to long-term Zn supplementation. However, despite all the above findings, there is a lack of evidence from clinical trials that Zn administration is of therapeutic value in patients with encephalopathy. A recent systematic review and meta-analysis reviewed oral Zn in the treatment of hepatic encephalopathy.[67] Four randomized controlled trials (including a total of 233 patients) were examined. Three studies showed evidence of improved cognitive functioning. Two studies reported that encephalopathy recurrence rates were lower in the Zn-treated group, but the findings did not reach statistical significance. Larger randomized controlled trials are needed to investigate the effect of Zn supplementation in patients with hepatic encephalopathy.

Marginal Zn Deficiency

Mild Zn deficiency is relatively common in European populations.[5,68] Although it does not cause overt clinical features, it can compromise cellular and humoral immunity, leading to increased susceptibility to infections.[69,70] There may be impaired growth and wound healing.[71] Neuropsychological performance may be impaired in children[72] and cognitive function reduced in the elderly.[73] It may also be a risk factor for premature atherosclerosis, but it is unknown whether supplementation influences outcomes in this condition.[74] Mild Zn deficiency has been demonstrated by studies that have observed improved growth or reduced infection rates following supplementation.[75,76] However, it is a difficult condition to diagnose in individual patients because of the lack of diagnostic criteria or reliable laboratory tests. Diagnosis requires a high index of suspicion and examination of the whole clinical picture to identify possible causes and consequences of Zn deficiency. The consequences of Zn deficiency are summarized in Table 2.

Markers of Zn Status

Currently, no single test reliably reflects whole-body Zn status. There is therefore an urgent need for reliable biomarkers, first, to enable diagnosis and management of deficiency in individual patients and, second, for studying its prevalence in the population.

Plasma Zn

A recent review of the available markers concluded that plasma Zn was the most useful.[77] It responds in a dose-dependent manner to dietary supplementation in subjects with low or moderate baseline status. However, its interpretation is confounded by a number of factors, which are discussed below.

First, plasma Zn is an insensitive marker for deficiency.[76] Adaptive mechanisms buffer changes in its concentration to changes in dietary intake. Consequently, hypozincemia occurs relatively late in deficiency once the size of the functional (exchangeable) pool is severely decreased. Even when deficiency is sufficiently severe to impair growth, plasma concentrations may remain within the reference range. However, when clinical symptoms consistent with severe deficiency are present, measurement of plasma Zn should be helpful diagnostically.

Second, hypozincemia can be caused by factors unrelated to Zn status. Plasma concentrations should be interpreted with caution in any situation where there is an APR, hypoalbuminemia, or hemodilution or during pregnancy in which there is physiologic plasma expansion.[38,78] Studies have investigated the extent to which the APR decreased plasma Zn. Minor illness (CRP < 15 mg/L) caused a 10% decrease, whereas major illness (CRP, 100–200 mg/L) caused a 40%–60% decrease.[42] In addition, plasma Zn decreases by about 50% within 6 hours of major surgery.[79] Unfortunately, it is difficult to predict the extent to which these factors affect plasma Zn in an individual, and unlike the plasma calcium concentration, no adjustment for albumin is possible. A recent study concluded that plasma Zn can be reliably interpreted only when the APR is mild (CRP < 20 mg/L).[80] When the CRP concentration is normal, hypozincemia can be interpreted more confidently as indicating deficiency. Factors causing hypozincemia are listed in Table 3.

Third, interpretation of plasma Zn is complicated by its high biological variation.[4] Limited weight should be attached

Table 3. Causes of Hypozincemia.

Cause	Mechanism
Severe zinc deficiency	Decreased intake, increased losses, adaptive mechanisms no longer able to compensate sufficiently
Estrogens, oral contraceptive pill, corticosteroids	Redistribution from plasma to cells
Stress, infection, inflammation	Redistribution from plasma to intracellular sites, increased urinary losses
Postprandial decrease	Redistribution of zinc to intracellular sites for anabolic use

to individual results. Regarding interpretation of serial results, critical difference calculations showed that a change in the plasma Zn concentration is unlikely to be significant (at 95% probability) unless it is above 30%. Changes smaller than this can be accounted for solely by biological variation. Clinicians should be alert to artifactual results when requesting plasma Zn. Its reliability depends on correct collection and storage of the specimen. Zn contamination of the specimen can occur from contact with gel separators, rubber, and heparin.[3] Collection tubes should therefore be approved by the trace element laboratory before use. Hemolysis can increase plasma Zn because erythrocytes have concentrations 5- to 10-fold higher than plasma. Guidance on specimen collection is available elsewhere.[81] In summary, plasma Zn lacks diagnostic sensitivity and specificity. However, its measurement can contribute to the diagnosis of overt Zn deficiency, providing that the APR is limited or absent.

Urinary Zn

During deficiency, the urinary Zn concentration is anticipated to decrease because of adaptation. An inappropriately increased concentration therefore suggests a urinary route of loss. However, urinary Zn has limited utility in the investigation of deficiency because it is affected by factors other than Zn status, such as catabolism.[82] In addition, urine collections may be inaccurate. It has been concluded to have utility as a marker only where there is moderate Zn status at baseline.[77] A reference range for urinary Zn excretion has been cited as 4.5–9.0 μmol (0.3–0.6 mg) per 24 hours.[3]

Other Markers of Zn Status

Zn is required for the growth-promoting effects of IGF-I and for restoration of plasma IGF-I concentrations.[9] This has led to interest in IGF-I as a marker of Zn status. Studies have shown that IGF-I is consistently decreased in Zn deficiency.[53] Zn intake correlated with the plasma IGF-I concentration in healthy postmenopausal women and remained its major determinant after adjustment for age, weight, and nutritional intake.[83] In studies of malnourished children, IGF-I increased following Zn supplementation.[84] These findings suggest potential utility for IGF-I measurement in the investigation and monitoring of Zn status. However, it lacks diagnostic specificity because it decreases in conditions other than Zn deficiency, including growth hormone deficiency and severe acute illness. If used in the assessment of Zn status, IGF-I should be considered in the clinical context so that confounding factors can be excluded.

Zn deficiency results in increased Cu absorption, leading to hypercupremia.[50] Hypercupremia and a Cu:Zn ratio of above 1.5 have therefore been suggested as biochemical markers of Zn deficiency. A number of other markers are not considered useful biomarkers—namely, polymorphonuclear cell Zn, platelet Zn, and alkaline phosphatase activity.[77] Plasma MT correlates with Zn status but is adversely affected by the APR. Numerous other markers have been suggested, including salivary Zn, erythrocyte MT, plasma superoxide dysmutase, lymphocyte Zn, carbonic anhydrase, and fecal Zn, but there are insufficient data available to reach conclusions on their utility. Given the wide variety of physiologic roles of Zn, it is likely that any biomarker used in isolation will be of limited value as a diagnostic test. Possible new approaches include deriving composite indices from panels of markers or developing metabolomic methods. Kinetic studies have been used in the evaluation of markers but are not practicable diagnostically in individual patients.

Zn and PN

In 1976, acute Zn deficiency was first reported in a patient receiving PN. It appeared after about 2 months of Zn-free PN, starting with a perioral rash that later became widespread.[85] These features were recognized as being attributable to Zn deficiency because of their similarity to features of untreated acrodermatitis enteropathica and the response to supplementation with 80–220 mg zinc sulphate daily.[86] To prevent deficiency, it is therefore important to supplement PN appropriately, especially when it is the sole means of nutrition support. However, it should be emphasized that the purpose of providing micronutrients is not solely to prevent clinical deficiency but to enable optimal metabolic functioning.

Worldwide, the number of patients suffering from PN-associated Zn deficiency is small compared to the number with dietary deficiency. However, the former are readily treated. It is therefore important that clinicians prescribing PN have a strategy for early detection of Zn deficiency so that it can be treated before clinical consequences occur. Patients

Table 4. Factors Predisposing to Zinc Deficiency in Patients Receiving Parenteral Nutrition.

Factor	Underlying causes
Preexisting deficiency	Low zinc intake, poor appetite, increased demands of growth, pregnancy or lactation
Decreased absorption	Decreased absorptive surface area, dietary inhibitors (phytic acid, iron), malabsorption, inflammatory bowel disease
Gastrointestinal tract loss	Diarrhea, fistula losses, stomal losses, nasogastric aspirates, chyle leaks
Urinary loss	Cysteine infusion, sepsis, drugs
Decreased delivery	Complex formation in parenteral nutrition solution, adherence to lines

requiring PN are at high risk of deficiency because multiple causes may be present simultaneously. There may be a nonfunctioning or inaccessible GI tract, as well as excessive losses from stomal sites, prolonged upper GI aspiration, or diarrhea.[87] The patient may be catabolic, and these problems may occur on a background of chronic malnutrition. The adaptive mechanisms are likely to be compromised because of intestinal failure, rendering the patient unable to compensate for losses.

Premature infants are at high risk of deficiency because of shortening of the final trimester of pregnancy, the period during which most Zn is normally transferred from mother to fetus. Neonates who have undergone surgery are also susceptible because surgical stress increases urinary Zn losses.[44] Urinary losses may also increase because of cysteine supplementation of PN. Additional cysteine is given to these infants in an effort to maximize parenteral calcium and phosphate provision but results in increased proximal tubular secretion of Zn.[88] A recent study of children with intestinal failure reported that Zn deficiency was the commonest mineral deficiency, occurring in 67% of patients.[89] In children on long-term PN requiring intestinal transplantation, Zn deficiency was one of the commonest micronutrient deficiencies posttransplant.[90] Possible reasons for this, as suggested by the authors, are increased loss from stomal outputs and increased utilization of Zn by high rates of mucosal turnover. The factors predisposing to Zn deficiency in patients receiving PN are summarized in Table 4. Where possible, these should be identified and treated.

As well as being at high risk for developing Zn deficiency, patients requiring PN are vulnerable to its consequences, including impairment of wound healing, delayed restoration of positive nitrogen balance postoperatively, and sepsis. Deficiency in neonates can also compromise their growth and functioning of the immune system. These problems do, however, respond to supplementation.[91,92]

Assessment of Zn Status in Patients Receiving PN

The results of clinical laboratory analyses should always be interpreted in the context of clinical findings and results of other investigations. This is particularly important in the case of plasma Zn concentrations in PN patients because of the many factors confounding interpretation. Plasma Zn may be a more reliable test in patients on home PN who are not acutely ill, but even in this situation, it lacks diagnostic sensitivity. The clinical assessment should seek GI disease and recent infections. It should assess GI losses, dietary intake, and the current supplementation regimen, if any. Macronutrient status should also be assessed. On examination, the presence of a skin rash should be noted and wound status assessed. CRP should be measured to assess the APR.

The gold standard method for diagnosis of Zn deficiency is the clinical response to treatment. A trial of treatment, followed by observation, should therefore be considered when the diagnosis is suspected. If deficiency is diagnosed, the possibility of other micronutrient deficiencies should be considered because they tend to coexist and have synergistic effects. For example, deficiencies of vitamin B_{12}, folate, or ascorbate can all contribute to poor wound healing and should all be considered. The multidisciplinary nutrition support team should include a member of the laboratory service who can advise on interpretation of tests and management of metabolic disorders such as Zn deficiency.

Supplementation of Zn in Patients Receiving PN

Studies have shown that plasma Zn decreases promptly in patients treated with Zn-free PN. Supplementation should therefore begin at or before commencement of PN. Ideally, supplementation would be achieved via the GI tract; however, the GI tract may be unavailable for use. Even when some enteral nutrition (EN) can be provided, micronutrient absorption may be unpredictable because of GI disease. The parenteral route of administration is the most reliable because it optimizes delivery. Under optimal conditions, bioavailability of parenteral Zn should be close to 100% but can decrease because of adherence to lines or formation of precipitates in the bag. Infused Zn can also be lost in the urine bound to albumin or organic ions.

Recommendations on parenteral Zn provision differ from the dietary reference intakes for oral feeding because patients receiving PN are likely to be sicker and have a preexisting deficit. Altered physiology of the GI tract may alter requirements by influencing Zn kinetics. Requirements may also increase during anabolism because of protein synthesis and tissue

growth. While standard recommendations are useful as a starting point during supplementation decision making, clinical judgment should be used because, in some situations, the actual requirement will be considerably higher. However, when patients are referred malnourished but with an intact and functioning gut, adaptation will ensure that the body is in a Zn-conserving state. In this situation, provided that there are no abnormal GI losses, provision of large amounts of Zn may be unnecessary.

The amount of Zn required in PN is a matter of ongoing debate. The daily requirement for Zn by parenteral administration has been estimated at 2.5–4 mg (38–61 μmol; per the American Gastroenterological Association).[93] More recently, the Task Force for the Revision of Safe Practice for Parenteral Nutrition (American Society for Parenteral and Enteral Nutrition) recommended 2.5–5 mg daily as a standard but stated that this was an approximation.[94] This amount is likely to be sufficient for most patients with normal stool losses. However, supplementation should be increased in proportion to the volume of GI fluid lost. It is estimated that patients with diarrhea who have an intact small bowel lose 15.2 mg of Zn per liter of enteric fluid, whereas patients with short bowel syndrome lose 3.6 mg of Zn per liter.[95] It has been recommended that 12 mg of Zn should be added per liter of diarrheal, stomal, or fistula losses.[96] Ideally, losses should be quantitated by direct measurement, but this is unlikely to be possible. A recent study of trace element dosing and monitoring in patients receiving home PN observed that an average Zn provision of 7.6 mg/d was sufficient to maintain normal plasma Zn concentrations for 90% of patients without short bowel syndrome, whereas patients with short bowel syndrome required 9.1 mg/d.[97]

Additional supplementation will be required in trauma or sepsis. It has been suggested that an additional 2 mg/d should be given during acute catabolism.[95] Supplementation above the basic requirement will also be required if there are clinical signs of deficiency or if plasma Zn is low in the absence of an APR. In patients with chyle leaks, Zn status should be assessed and consideration given to additional supplementation. In patients considered to be at risk of refeeding syndrome, it may be appropriate to give a loading dose of 10–30 mg of Zn, followed by the daily maintenance dose.[60] The actual rate of delivery of Zn will depend on the starting rate of the PN bag, which in turn will depend on the risk of refeeding complications. The starting rate should therefore be considered when the decision is made regarding how much Zn to add to the PN.

In children, Zn requirements depend on growth rate. Recommendations on supplementation therefore relate to age. Infants require more Zn per kilogram of body weight than do adults, but proportionately less is required as infancy progresses.[94,96] Preterm infants require 400 μg/kg/d; term infants (<3 months of age), 250 μg/kg/d; term infants (>3 months of age), 100 μg/kg/d; and children, 50 μg/kg/d (maximum, 5000 μg/d).[44,97,98] When PN is supplemental rather than total or where its duration is limited to <4 weeks, Zn is the only trace element that should be given. Other trace elements are not considered necessary until 2 weeks of age. As in adults, individualization of supplementation may be appropriate.

In recent years, there has been much concern about the clinical implications of shortages of PN additives, including both multi– and individual trace element products. Zn is among those that have been in short supply since 2010.[99] This is of concern given that its omission from PN can quickly result in deficiency. This problem was illustrated by a recent case of a PN-dependent patient in whom Zn was withdrawn because of a shortage of a multi–trace element product.[100] Zn deficiency occurred 29 days later. Fortunately in this case, it was possible to supplement Zn orally. The American Society for Parenteral and Enteral Nutrition has recently provided guidance on managing PN product shortages.[101] Briefly, micronutrients should be given orally or enterally where possible, and to conserve supplies, the practice of adding injectable minerals to enteral products should be avoided. Prioritization to receive supplementation should be given to the most vulnerable patients, such as those with preexisting clinical deficiency. However, decisions on prioritization of resources should be made locally. Nutrition support teams are well placed to do this because of their familiarity with local protocols and with the nature of the local clinical workload. Approaches that have been taken to conserve resources, as reported by an American Society for Parenteral and Enteral Nutrition survey, include decreasing micronutrient supplementation to thrice weekly or giving 50% of the recommended dose daily.[101] Advice has been published on strategic planning for future product shortages.[102]

Monitoring Zn Status in Patients Receiving PN

Guidance on nutrition support in adults per NICE (National Institute of Health and Care Excellence, UK)[103] recommends that Zn concentrations are checked at baseline and every 2–4 weeks thereafter depending on results. It is advisable to measure the concentration 1–2 weeks after a change in dose, irrespective of the duration of PN. In patients receiving long-term PN in whom stability has been achieved, concentrations should continue to be checked periodically. Monitoring of Cu may be helpful because hypercupremia or increased Cu:Zn ratio suggests Zn deficiency.[50] Patients should also be monitored clinically to assess GI losses and possible signs of clinical deficiency.

Zn Toxicity

Parenteral delivery of Zn bypasses physiologic control of uptake. Consequently, there is the potential for toxicity to arise if excess is infused. It can present acutely with symptoms of nausea, vomiting, and diarrhea or less acutely as hypocupremia, decreased plasma ceruloplasmin, microcytic anemia,

neutropenia, impairment of the immune system, and decreased plasma HDL cholesterol concentration.[104] Toxicity could occur if a plasma Zn result is misinterpreted during the APR and excessive supplementation given. However, in practice, toxicity is unlikely in hospitalized patients receiving PN. First, Zn has relatively low toxicity compared to other trace elements. The efficiency of its excretion into bile and intestinal secretions may help protect against toxicity. Second, the duration of PN in most hospitalized patients is short, usually <2 weeks. Toxicity is more likely in patients on home PN receiving high-dose supplementation for prolonged periods, especially if components of the PN are contaminated with Zn. For this reason, it is advisable to monitor Zn regularly in patients receiving long-term PN.[75] To ensure early detection of toxicity, plasma Zn should be measured along with Cu and a full blood picture.

Stability Considerations

During compounding of PN solutions, trace elements are usually added to the admixture as part of a multi–trace element mixture. To optimize stability, this is the final addition made before infusion. Precipitation can occur as a result of binding to organic ions, especially if the PN is stored.[105] Avoidance of precipitation and other stability problems therefore requires limits to be placed both on the size of the additions and on storage time. Compatibility of components should be checked with the local aseptic unit and, if necessary, with the manufacturer. Unfortunately, the commercially available multi–trace element mixtures have limited flexibility for meeting individual requirements. For example, in some patients with large Zn requirements, sufficient provision of Zn may result in excessive delivery of manganese (Mn).[94] A recent review of parenteral trace element provision in children has recommended prescription according to individual requirements and revision of use of multi–trace element products.[106] To meet large requirements, it is sometimes necessary to give Zn or other trace elements by a separate infusion. There is a need for a wider variety of products to be made available to improve flexibility when prescribing supplements.

Zn in EN

While this review focuses on PN, it is appropriate to consider EN briefly. Zn should be given orally or enterally where possible. Its administration via the GI tract enables absorption according the body's requirements and, unlike PN, avoids bypassing physiologic controls. Zn supplements can be given by mouth in patients receiving PN, even to those with significant stomal losses, as long as the stomach and duodenum are intact.

Standard EN products contain sufficient micronutrients to meet daily requirements in accordance with the RDA. However, RDAs apply to the healthy population and may be insufficient for many patients. Patients' requirements may be increased because of a preexisting deficit, increased losses, or increased demands. In contrast to intravenous infusion, enteral delivery of Zn does not guarantee its delivery to tissues. Bioavailability decreases if there is decreased absorption. For example, following small bowel resection, there is decreased Zn absorption because of decreased absorptive surface area and shorter transit time. Even where the duodenum and jejunum are intact, intestinal reabsorption of secreted Zn will be decreased if other parts of the small bowel are diseased or have been resected. In critically ill patients, absorption may be suboptimal because of GI conditions, such as ileus or ischemia. Other factors that can decrease Zn absorption include excessive calcium and iron intake and treatment with bisphosphonates. High-dose enteral Zn supplementation can impair Cu absorption, and so Cu should be given along with Zn.[107] When the full requirements of nutrients cannot be met enterally, supplemental PN may be required. In this case, it should be ensured that the Zn content of the total feed is sufficient to meet requirements.

There are relatively few reports of Zn deficiency occurring in enterally fed patients. However, clinically overt deficiency has been reported in patients receiving EN in whom the level of Zn provision had been considered sufficient to meet requirements.[108-110] These cases emphasize the importance of continuous monitoring of patients on long-term EN and keeping Zn provision under close review.

Future Directions

Knowledge of Zn as a nutrient has advanced considerably since PN was introduced in the 1970s. However, there are still many unknowns. There is limited understanding of Zn metabolism in illness and starvation. Further study is needed into the role of Zn status in refeeding complications and how its assessment can be incorporated into assessment of refeeding risk. There is a limited understanding of how its deficiency interacts with coexisting micronutrient deficiencies. Future studies need to consider micronutrients collectively.

Better tests of Zn status are required so that its assessment can become more objective. It is possible that future tests will be based on measurement of Zn-activated gene transcription and mitogenic signal transduction. Such tests would be anticipated to be sensitive because they are based on processes that become impaired before plasma Zn concentrations or enzyme activity decrease. Given that mild Zn deficiency can compromise the immune system, it may be possible to develop tests based on immune functioning. Functional tests could also be developed on the basis of Zn proteins and metalloenzymes. In addition, proteins of the insulin-like growth factor system are worthy of further investigation as tests. Panels of biomarkers could provide reliable assessment of Zn status. It is likely that as the "-omics" technologies progress, this will lead to the development of tests enabling accurate assessment of Zn status. Individualization of treatment may follow, ultimately superseding standard recommendations on Zn supplementation.

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