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On the Assessment of Trace Mineral Nutriture in Patients on Total Parenteral Nutrition

Practitioners and nutritionists have developed an increasing awareness of the importance of trace minerals in human nutrition. Observation of iatrogenic deficiency of one or another trace element in patients undergoing total parenteral nutrition (TPN) has served to reinforce this concern. It is important to maintain a vigilance and to anticipate the possibility of impaired trace mineral nutriture in patients on TPN. At present, 14 trace elements have been linked to nutritional roles in mammalian species—and presumably in man—and of these, 10 are considered to be essential (*Table I*). This review concentrates on the *mineral* elements. With the accumulated experience of the past decade, a few practical guidelines for the assessment of trace mineral nutriture in patients on TPN will be outlined in the present report.

Causes of Trace Mineral Deficiency in Patients on TPN. There are two possible causes which, alone or in combination, can contribute to impaired trace mineral nutriture during TPN:

Table I: Trace elements essential in mammals.

Iron	Iodine
Zinc	Fluorine
Copper	Molybdenum
Manganese	Cobalt
Selenium	Nickel
Chromium	

- Pre-existing, underlying disorders may predispose to depletion of one or more trace minerals;
- Some factor(s) intrinsic to the TPN regimen itself may impair trace mineral nutriture.

Figure 1 illustrates the possible mechanism for interference with trace mineral delivery or metabolism during TPN. Minerals can be diverted from the circulation for use at the tissue level. A nutritionally-related or disease-related fall in serum-binding proteins can interfere with the transport of minerals. Enhanced excretion of a mineral may occur due to changes in renal or gastrointestinal physiology related to TPN. All these mechanisms are possible, but experience has taught us that a reduction in intake of minerals due to a lack of sufficient delivery from the intravenous alimentation solutions is by far the leading cause of trace mineral deficiency during TPN.

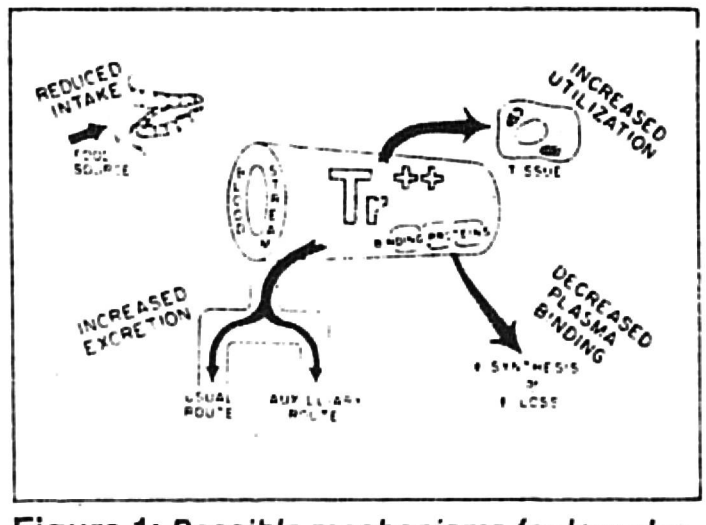

Figure 1: ***Possible mechanisms for low plasma trace metal concentrations with total parenteral alimentation.***

Iron. Iron is perhaps the most difficult nutrient to lose from the body. With no ready route of excretion, only substan-

Table II: Clinical manifestations of human iron deficiency and laboratory indices for assessing iron nutriture.

Clinical manifestations
Fatigue
Listlessness
Exertional dyspnea
Headache
Paresthesias
Burning sensation of tongue
Altered attention span
Pica (?)
Pallor
Glossitis
Tachycardia
Koilonychia (rare)
Splenomegaly (rare)
Laboratory Indices
Hemoglobin*
Hematocrit*
Red cell indices*
Peripheral smear*
Serum iron**
Transferrin saturation**
Free-erythrocyte protoporphyrin**
Serum ferritin**
Stainable bone marrow iron***
Radioiron absorption test***

*Not specific for iron deficiency.
**Four most practical assays.
***Excessively invasive for routine application.

Table III: Diseases predisposing to zinc depletion and clinical manifestations of human zinc deficiency.

Diseases
Alcoholism
Alcoholic cirrhosis
Alcoholic pancreatitis
Inflammatory bowel disease
Celiac disease
Short bowel syndrome
Jejuno-ileal bypass
Pancreatic insufficiency
Cystic fibrosis
Nephrotic syndrome
Hemolytic anemia
Anorexia nervosa
Chronic uremia
Clinical manifestations
Growth retardation
Hypogonadism
Alopecia
Skin lesions
Diarrhea
Immune deficiencies
Behavioral disturbances
Night blindness
Impaired taste acuity
Impaired wound healing
Hypospermia

tial blood loss can reduce total-body iron. The fully-repleted adult has about 1 g of iron in available iron-storage reserves, enough to replace one-third of the iron contained in red cells of a non-anemic individual. Disease requiring TPN may, however, have resulted in a chronic or acute loss of blood. In this case, *therapeutic* iron in addition to maintenance iron would be indicated.

Clinical manifestations of iron deficiency are given in *Table II*. Pallor and exertional dyspnea are common findings in iron deficiency anemia although they are not specific to that disorder. Paresthesias and headache are related to tissue deficiencies but again are not pathognomonic of iron deficiency. Laboratory indices for assessing iron nutriture in man are listed in *Table II*. Under usual circumstances of iron depletion, ferritin levels decline first. A decline in serum iron and an increment in free erythrocyte protoporphyrin are next in sequence. Only finally does the red cell mass begin to shrink. In patients on TPN, other reasons for a low hemoglobin and a reduced red cell volume must be considered. Thus to assess iron status, the biochemical indices must be relied upon. Low levels of circulating transferrin only produce a false reduction in iron concentration. The presence of an active and appropriate reticulocyte response to a reduction in red cell volume is a reasonable indication that the nutritional factors for erythropoiesis, including iron, are available to the bone marrow.

Zinc. A number of diseases that result in a need for TPN also predispose to zinc depletion. A list of some such diseases is given in *Table III*. The findings of Wolman et al. have emphasized the importance of gastrointestinal fluid loss as a contribution to zinc depletion, especially in inflammatory bowel diseases.[1]

The clinical manifestations of zinc deficiency are listed in *Table III*. The first two listed are unlikely to relate to usual situations during TPN since they involve only prepubescent children. In long-term home alimentation in a child, however, these manifestations could arise with the development of chronic zinc deficiency. By far the most commonly recognized findings in acute zinc deficiency in all ages are hair loss and skin lesions. The cutaneous changes seen in zinc deficiency have been diverse, variously described as eczematous, seborrheic, bullous, and acrodermatitis-like. It is important to recognize that essential fatty acid depletion, another deficiency syndrome that can occur with a poorly managed TPN regimen, is characterized by scaly skin lesions. Immune deficiencies and behavioral disturbances are probably as common in occurrence in patients with zinc deficiency on TPN, but much less frequently looked for. Simple tests for taste acuity[2] and dark adaptation[3] have been reported and could be used to quantify the hypogeusia and night blindness, respectively, in monitoring patients during protracted courses of TPN.

A prodigious number of laboratory tests, both biochemical and functional, have been used clinically or investigationally in the assessment of zinc nutriture (*Table IV*). Most have serious limitations[4]; two of the promising functional tests were mentioned earlier. The mainstay for the assessment of zinc status has been the determination of plasma or serum zinc concentration.[4] It has a number of inherent pitfalls (*Table IV*). However, in the *serial* monitoring of a given individual on TPN, a *progressive* fall in zinc concentration usually reflects inadequate intake of the nutrient. Some investigators[5-7] have reported that a decline in serum alkaline phosphate activity often heralds the onset of zinc deficiency manifestations. Urinary zinc excretion data is unreliable as a diagnostic aid in assessing zinc status. Some situations associated with the use of TPN, such as surgery, trauma, and burns, produce hyperexcretion of zinc. Quantification of this loss through 24-hr urinary collection for zinc analysis may aid in adjusting the supplemental dose of zinc.

Table IV: Laboratory indices for assessment of zinc nutriture and pitfalls in the use of circulating zinc levels in evaluation of zinc nutriture.

Laboratory indices	
Plasma or serum zinc concentration	
Erythrocyte zinc content	
Leukocyte zinc content	
Hair zinc content	
24-hr urinary zinc excretion	
Serum alkaline phosphatase	
Erythrocyte carbonic anhydrase	
Serum ribonuclease	
Serum retinol-binding capacity	
Taste acuity	
Zinc-65 turnover and pool size	
Zinc balance	
Skin zinc concentration	
Fingernail zinc concentration	
Sweat zinc concentration	
Neutrophil or macrophage chemotaxis	
Red cell zinc-65 uptake *in vitro*	
Retinal dark adaptation	
Pitfalls	
Condition	***Error***
External contamination	False increase
Hemolysis	False increase
Veno-occlusion in sampling	False increase
Prolonged fasting	False increase
Estrogens, oral contraceptives	False decrease
Corticosteroids	False decrease
Infection/inflammation	False decrease
Postprandial sampling	False decrease
Serum protein concentration	Either direction
Serum protein binding-affinity	Either direction

Table V: Diseases predisposing to copper depletion and clinical manifestations of copper deficiency.

Diseases
Short bowel syndrome
Jejuno-ileal bypass
Celiac disease
Tropical sprue
Nephrotic syndrome
Clinical manifestations
Anemia
Neutropenia
Skeletal demineralization*
Depigmentation of hair and skin
Defective elastin formation, (aneurysms)
Central nervous system abnormalities
Hypotonia
Hypothermia

*Only present in individuals (children) with *growing* bones.

Copper. A number of patients coming to TPN have an underlying disorder that predisposes to copper depletion; these are enumerated in *Table V,* along with the clinical manifestations of zinc deficiency observed in patients on TPN. Only rapidly growing bone is susceptible to demineralization. Radiographic appearance is reminiscent of scurvy and there has been speculation that copper has a role in ascorbic acid metabolism.[8] The most valuable diagnostic features of copper deficiency during TPN are neutropenia and a microcytic, hypochromic anemia.[9] In the latter circumstance, iron deficiency must be ruled out as a cause of the anemia. When the anemia is predominantly due to copper depletion, a brisk reticulocytosis often accompanies copper supplementation.

The laboratory indices for determining copper status are listed in *Table VI.* As with zinc, serum and plasma copper determinations are subject to pitfalls. However, as with zinc, serial determination during the course of intravenous alimentation is useful. Some 94% of circu-

Table VI: Laboratory indices for assessment of copper nutriture.

Hemoglobin concentration
Packed cell volume (hematocrit)
Reticulocyte count
White cell count and differential
Plasma or serum copper concentration
Erythrocyte copper content
Hair copper content
Serum ceruloplasmin
Erythrocyte superoxide dismutase
Serum amine oxidase
Leukocyte cytochrome-c oxidase
Copper-64 or copper-67 turnover
Copper balance
Fingernail copper concentration
Skin elastin morphology

Table VII: Clinical manifestations of selenium deficiency and laboratory indices for assessment of selenium nutriture.

Clinical manifestations
Myalgia and muscle tenderness (?)
Increased red cell fragility (?)
Pancreatic degeneration (?)
Increased susceptibility to cancer (?)
Laboratory indices
Plasma or serum selenium concentration
Whole blood selenium concentration
Erythrocyte selenium concentration
Erythrocyte glutathione peroxidase
24-hr urinary selenium excretion
Red cell selenium-75 uptake *in vitro*

lating copper can be accounted for by copper in ceruloplasmin. Serial ceruloplasmin determinations can usually serve as a surrogate for copper determinations in hospital practice. Most of the methods listed in *Table V*—with the notable exception of hematological tests—find little practical application in assessing copper status in patients on TPN.

Selenium. Selenium has been recognized in the past decade as an essential component of mammalian glutathione peroxidase, an enzyme which protects cells against endogenous and exogenous antioxidant stress.[10] Various forms of cancer apparently impair selenium nutriture.[11] The clinical manifestations imputed to human selenium deficiency are listed in *Table VII*. None has been rigorously confirmed. In patients undergoing TPN with selenium-deficient alimentation solutions, muscle pain and muscle tenderness were noted; these signs and symptoms responded to selenium supplementation.[12] Practitioners should remain attuned to this constellation of findings in patients on TPN. The biochemical indices of potential value in assessing selenium status are listed in *Table VII*. Several studies have shown a common tendency for circulating selenium levels to decline during TPN.[12,13]

Chromium. Chromium is believed to be the elemental component of "glucose tolerance factor," a soluble moiety believed to participate in insulin binding. Clinical manifestations described for chromium deficiency are illustrated in *Table VIII*; all features seem to be related to impaired glucose tolerance and have been reported in patients undergoing TPN.[14,15] Biochemical determination of plasma or serum chromium values has been notoriously difficult due to technical analytical problems. Neutron activation analysis, a procedure available at only a few institutions, offers the most

Table VIII: Clinical manifestations of chromium deficiency.

Glucose intolerance
Peripheral neuropathy
Metabolic encephalopathy
Increased susceptibility to cardiovascular disease

precise and accurate determination. Thus valid confirmation of a chromium-deficiency syndrome may be difficult.

Molybdenum. The essentiality of molybdenum for man is still being debated. In other mammalian systems, molybdenum is a component of enzymes involved in oxidation-reduction reactions involving organic sulfur (sulfite oxidase) and metabolites of degraded nucleic acid (xanthine oxidase). Recently, an abstract appeared reporting a patient on prolonged TPN who experienced a complex of clinical features (*Table IX*). The manifestations resolved with the administration of inorganic salts.[16] Physicians should be aware of this experience, as confirmatory observations are needed to assess the prevalence and importance of molybdenum deficiency in TPN.

Conclusions and Recommendations. Trace elements are no longer nutritional curiosities. Trace mineral deficiencies occur with frequency in patients on TPN. Failure to infuse sufficient amounts of the distinct mineral nutrients to meet both losses from previous or ongoing illness or injury and the normal maintenance requirements is the most common cause of trace mineral depletion in such patients. A conscious *prospective* program of clinical and laboratory assessment including serial evaluation of the signs, symptoms, biochemical parameters and functional tests discussed should be instituted in each individual undergoing TPN. Furthermore, each member of the nutrition support service team should develop a habit of being *trace mineral*-minded in response to untoward clinical manifestations that might occur during the course of TPN. A systematic approach to administering trace minerals by parenteral routes is beyond the scope of this article but it has been discussed in detail in a recent report from the American Medical Association.[17] Adequate trace mineral nutriture should be a goal in the treatment of each patient undergoing TPN. Use of the information outlined here should help this goal become a practical reality in your hospital and practice.

Table IX: Clinical manifestations of molybdenum deficiency.

Headache
Night blindness
Irritability
Lethargy
Coma
Abnormal metabolism of sulfur amino acids
Abnormal purine degradation

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