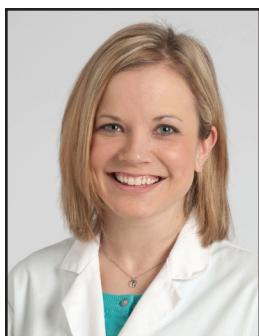


Trace Element Supplementation and Monitoring in the Adult Patient on Parenteral Nutrition



Cassandra Pogatschnik

Trace elements are essential nutrients for the long-term parenteral nutrition (PN) patient. Though often overlooked by medical providers, they play a significant role in human metabolism and can lead to serious complications when deficient or in excess. Individual trace element regimens are determined by patient presentation, organ dysfunction, inflammation, and patient history. Laboratory studies are used strictly as a guideline to establish trends due to their unreliability in predicting true nutrient status. Awareness of the complexity of trace elements and an understanding that careful monitoring of trace element status can improve patient success on PN are essential.

INTRODUCTION

As an integral and often life sustaining therapy, parenteral nutrition (PN) enables absorption of nutritive constituents while bypassing the gastrointestinal (GI) tract. Macronutrients sustain an individual calorically; electrolytes allow for proper electrical charge and cellular space fluid distribution; and micronutrients allow for efficient human metabolism. Often overlooked by clinicians, trace elements regulate metabolism as enzymatic cofactors that transport substrates across cell membranes.^{1,2} In the United States five of nine essential trace elements are supplemented in PN. Routine addition and adjustment of chromium, copper, manganese, selenium and zinc are based upon laboratory

levels, where appropriate, as well as physical and clinical symptoms of deficiency and toxicity. Specific populations, including the severely malnourished, patients with high enteral losses and those on long-term home PN, require trace element monitoring.

Trace Element History

Since PN's birth in the 1960s and its introduction to the home setting in the early 1970s, trace elements' importance was recognized. In 1977 an expert nutrition panel from the Nutritional Advisory Group of the American Medical Association (NAG-AMA) devised the first trace element guidelines which were submitted to the Food and Drug Administration (FDA) in 1978 and were subsequently published in the *Journal of American Medicine* in 1979.^{3,4} (See Table 1) At that time it was encouraged that single formulations of individualized

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Table 1. Multi-trace (MTE) Formulations Available in the United States Currently

Trace Element	DRI Dietary Reference Intake	Parenteral FDA Guidelines	A.S.P.E.N. Most Recent Proposal	MTE-4C (per 1 mL) American Regent	MTE-4 (per 3 mL) American Regent	MTE-5C (per 1 mL) American Regent	MTE-5 (per 3 mL) American Regent	Addame! N (per 10 mL) Fresenius Kabi
Chromium	20-35 mcg	10-15 mcg	Omit or <1mcg	10 mcg	12 mcg	10 mcg	12 mcg	10 mcg
Copper	0.9 mg	0.5-1.5 mg	0.3-0.5 mg	1 mg	1.2 mg	1 mg	1.2 mg	1.3 mg
Fluoride	3-4 mg	Not routinely added	n/a	n/a	n/a	n/a	n/a	0.95 mg
Iodine	150 mcg	Not routinely added	n/a	n/a	n/a	n/a	n/a	0.13 mg
Iron	8-18 mg	Not routinely added	n/a	n/a	n/a	n/a	n/a	1.1 mg
Manganese	1.8-2.3 mg	0.15-0.8 mg	0.055 mg	0.5 mg	0.3 mg	0.5 mg	0.3 mg	0.27 mg
Molybdenum	45 mcg	2.5-5 mg	n/a	n/a	n/a	n/a	n/a	19 mcg
Selenium	55 mcg	20-60 mcg	60-100 mcg	n/a	n/a	60 mcg	60 mcg	0.13 mg
Zinc	8-11 mg	3-4 mg	No change	5 mg	3 mg	5 mg	3 mg	6.5 mg

trace elements be available for easier adjustment and removal as necessary.^{4,5} Selenium was established as essential in 1979 when supplementation eradicated Keshan Disease (a congestive cardiomyopathy caused by a combination of dietary deficiency of selenium and the presence of a mutated strain of Coxsackie virus characterized by heart failure and pulmonary edema). This prompted selenium's inclusion, and supported copper dosage reduction (based on copper balance studies in long-term PN patients) in the 1982 trace element review.⁴ Despite numerous expert panel reviews, studies, and proposals, the FDA has not yet approved a new multi-trace element formulation, a delay that may prove hazardous in some patients.³ One recent investigation performed autopsies on 8 PN dependent patients for an average duration of 14 years who had received the NAG-AMA trace element formulation. The autopsies revealed excessive tissue concentrations of chromium, copper, and manganese, which supported the need for change in multi-trace formulations today.⁶

Monitoring Trace Elements

With optimal doses under debate, PN drug shortages, a growing long-term PN population, variability of patients' conditional requirements, and questionable laboratory testing, the task of monitoring home PN patient's micronutrient status is difficult. Trace element lab samples are difficult to collect, handle, and are extremely susceptible to contamination, making them an infrequent and expensive physician order.² When obtained, trace element results must be interpreted with caution as some are affected by inflammatory states.² If the clinician is uncertain, but *suspects* an inflammatory or infectious process (such as active Crohn's, etc.) may be present, while there are no data to support this practice, checking a C-reactive protein might be considered (See Table 2). Measurements of serum and plasma levels have demonstrated to be less indicative of body stores or nutrient adequacy in those receiving PN.⁶ Decreased laboratory levels may actually reflect redistribution versus true deficiency.⁷

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Trace Element Lab	Positive Acute-Phase Reactant	Negative Acute-Phase Reactant	Lab value effect with elevated CRP	Other Conditional Effects
Chromium (plasma)		X	↓	
Copper (serum) Ceruloplasmin (serum)	X		↑	↑ pregnancy, malignancy, liver disease, myocardia-infarction
Manganese (whole blood)		X	↓	
Selenium (plasma)		X	↓	
Zinc (serum)		X	↓	

Though whole blood and serum markers have shown unimpressive correlation to tissue levels,² they allow clinical establishment of patient baseline and trends. Suggestion for monitoring varies per clinician and home nutrition support program, however, it is suggested that trace elements be repeated at least annually. Upon trace element shortage (particularly when an individual supplement is omitted) or patient history of deficiency or toxicity, studies may be repeated every three months until levels and/or clinical symptoms improve. They may be repeated more frequently based upon clinical judgment. It is essential that clinicians confirm laboratory findings with both clinical and physical characteristics of deficiency and toxicity (See Table 3).

Chromium

Chromium is a transitional metal that is biologically active in the trivalent phase.² Considered an essential trace element due to its regulatory properties and decline with age, chromium gets incorporated into a chromodulin or “glucose tolerance factor,” promoting insulin action in peripheral tissue and reducing insulin requirements.^{2,8} Transported by transferrin and albumin, it competes with iron for binding sites on transferrin.^{2,8} Hemochromatosis is thought to be associated with both chromium deficiency and glucose intolerance.⁸ Deficiency symptoms include

hyperglycemia, hyperlipidemia,⁸ neuropathy,⁹ and in rare cases encephalopathy.¹⁰ It is important to note, that additional chromium supplementation will not improve hyperglycemia if it is already being adequately supplemented.² No toxicities have been reported in adults;^{3,9} however expert concerns arise from accumulation of high levels of chromium in the sera and tissue overtime. It has been proposed that efficient chromium dosing may be provided from alternate ingredient contamination, such as 70% dextrose solutions used for compounding PN formulations.³ Current recommended dosage of 10-15 mcg/day may be overestimated and new recommendations may be as low as 0.14-0.87 mcg/day.³ Removal from formulations may be preferred in patients with renal insufficiency as it is excreted most readily through urine.^{2,3,7,8} No satisfactory test has been discovered for measurement of chromium; however, with improved analytical measurements and quality controls, serum chromium can be measured more accurately. The best way to capture deficiency may be to monitor glucose response to chromium.¹¹

Copper

Copper allows for erythrocyte synthesis, absorption and use of iron, phospholipid formation, and improves connective tissue integrity.^{2,12} Transcuprein and albumin

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transport copper to the liver where it is incorporated into ceruloplasmin, which transports copper to peripheral tissues. Sixty to ninety-five percent of circulating copper is present in this form. Copper is not present in the blood due to poor solubility and must be drawn as a serum lab draw. Revealed during significant deficiency, and in patients with compromised GI tract with high enteric losses,¹³ symptoms include, leukopenia, hypochromic and normocytic anemia with depressed reticulocyte count.^{2,10} If left untreated, patients may present with gait difficulty, resembling Vitamin B12 deficiency,^{4,13} connective tissue disorders, blood vessel defects, osteoporosis, and cardiac disease.¹² Menkes Disease is defined as copper accumulation in the intestinal mucosa, which inhibits transportation of copper to the liver and tissue resulting in true deficiency, and in rare cases, causing degenerative brain disorders, severe mental retardation and in few instances, death.¹⁰ One case report revealed severe copper deficiency after a three-month intravenous multi-trace holiday due to intravenous product shortage.¹³ The multi-trace contained 0.5 mg copper/day, of which the patient received 5 days/week. Upon removal, the patient was supplemented with an oral multivitamin/mineral supplement containing 15 mg copper/day; of which she only took 1-2 doses/week due to GI intolerance. She presented with fatigue, lower extremity edema, WBC 3.1K, hemoglobin 6.5 g/dL and hematocrit of 21.3%. The patient was subsequently admitted and underwent a neurological exam and GI work-up, both of which were negative. Further labs concluded copper deficiency (Cu <3 mcg/dL, ceruloplasmin <3 mg/dL, and normal Zn of 61 mcg/dL). The patient was started on 6 mg oral copper for 1 week, 4 mg oral copper for 2 weeks, and then dosage was decreased to 2 mg/day. Two months later intravenous multi-trace was again available and was added back to the PN. Within two months all laboratory studies had normalized. Copper deficiency can manifest as early as eight to ten weeks upon withholding supplementation and with adequate repletion, can reverse hematological changes in one to two weeks.¹³ A case report by Spiegel et al. also demonstrated copper deficiency (confirmed by both lab and bone marrow biopsy) and pancytopenia eight weeks after intravenous copper removal.¹⁴ Repletion with copper sulfate improved the patient's hematological and copper studies; however, the patient expired from cardiac tamponade. Interestingly no reports of human

myocardial deaths caused by copper deficiency have been reported, however copper deficient rats have developed fatal cardiac diseases (ruptured arterial aneurysms and hemorrhagic pericardial tamponade) thought to be attributed to copper's effect on elastin and collagen synthesis.¹⁴ As a trace element that is almost exclusively excreted through the bile, cholestasis can lead to copper toxicity, and toxicity can cause hepatocellular damage, accumulation and cirrhosis.^{2,10} Blaszyk et al. studied long-term PN patients' hepatic tissue copper levels and compared them to patients with alternative drug induced cholestasis. Results concluded that PN patients who had significant cholestasis accumulated high levels of hepatic copper and found that PN therapy duration alone was independent of copper toxicity.¹⁵ Renal failure and neurological disorders have also been associated with copper toxicity.² Current recommended dose is 0.5-1.5 mg/day,¹² with 1 mg/day being provided in multi-trace formulations.³ The American Society for Enteral and Parenteral Nutrition (ASPEN) most recently proposed a dosage decrease to 0.3-0.5 mg/day.³ It is suspected that requirements may increase by 0.4-0.5 mg/day in persistent malabsorptive states^{12,13} and that a decrease in dosage to 0.15 mg/d or removal altogether may be required in cholestasis.¹⁶ Of note, it is necessary to monitor patients with such minute dosages as they have demonstrated pancytopenia at six weeks.⁹ Elevated bilirubin of 10.9 mg/dL and liver biopsy revealing mild steatosis, early fibrosis, and cholestasis prompted intravenous copper removal in another case report by Fuhrman et al.¹⁷ Fifteen months after removal, the patient required monthly red cell transfusions accompanied by WBC and platelet decline. Nineteen months after the copper holiday, bone marrow biopsy proved suspicion for copper deficiency etiology. Dosage of 1mg/day was again supplemented, copper levels rose and neutropenia and thrombocytopenia dramatically improved, resulting in a break from transfusions. Subsequently serum copper became elevated and was again removed. Three months later patient developed severe copper deficiency correlating again with neutropenia, thrombocytopenia, anemia, and again necessitating red cell transfusions. As a result of this experience Fuhrman et al. monitors serum copper quarterly and supplements 1 mg copper thrice weekly.¹⁷ Though serum copper and ceruloplasmin do not have high correlation with actual tissue accumulation, it is extremely important to monitor with the onset of clinical

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symptoms (see above). Autopsies have demonstrated copper accumulation in both liver and kidney without reflection in laboratory status.^{6,9} Smoking, pregnancy, and contraception were found to alter levels.^{10,11}

Manganese

Manganese is a cofactor in many enzymatic systems and has roles in bone formation and metabolism of carbohydrates and cholesterol.¹⁸ This enzyme is involved in fatty acid and protein synthesis as well as melanin and dopamine production.¹⁹ After oxidation in its trivalent form, manganese is bound to transmanganin and is successfully deposited in the liver, skin, and skeletal muscle.² Deficiency has not been well detected;² however weight loss, transient dermatitis, and occasional nausea and vomiting have correlated with low manganese levels.¹⁰ Intravenous manganese administration is recommended at 60-100 mcg/day while standard multi-trace formulations contain 500-800 mcg/day. Toxicity has been reported in patients receiving long term PN. Manganese has been shown to accumulate in the basal ganglia resulting in neurotoxicity^{2,9} and Parkinson's like symptoms, hallucinations, and agitation.¹⁰ Manganese toxicity may also be associated with liver toxicity and hepatic cholestasis.^{9,20} Laboratory levels often take five to six months to decrease when elevated.² One case reported an ongoing elevation of whole blood manganese for 369 days after complete removal of manganese; the patient had cholestatic disease.⁹ It has been recommended that manganese dosage be held in patients with hepatic dysfunction and cholestasis as it is almost exclusively excreted through bile;² however there is no evidence to support that manganese must be removed from PN in the setting of transient elevations of bilirubin in an acute care setting –this is not to say that evidence may be forthcoming, but clinical monitoring of these patients is essential. One study in Japan demonstrated that 55 mcg/day sustained serum manganese levels; with this evidence ASPEN supports dosage lowering to 55 mcg/day to prevent toxicity.³ Though lower than the US formulations, European dosing is 265 mcg/day and toxicity continues to exist.³ Whole blood manganese (a better representative of tissue manganese versus serum), found to be present in 60-80% of erythrocytes^{2,9} may be drawn annually and more often in patients with hepato-biliary dysfunction and/or in patients exhibiting clinical signs and symptoms of deficiency and toxicity (See Table 3).

Selenium

Selenium is needed to synthesize selenocysteine, which aids in glutathione peroxidase that serves as an antioxidant, protecting cell membranes from lipid peroxidases, and free radicals. Selenium also drives endocrine enzyme function, which regulates thyroid hormone and metabolizes vitamin C.^{2,21} Deficiency symptoms include macrocytic anemia, skeletal muscle pain and tenderness, arrhythmia, whitened nail beds, and loss of hair and skin pigmentation.^{2,21} The development of Keshan disease (see trace element history above) is due to severe selenium deficiency, which is characterized by severe cardiomyopathy that is often irreversible or fatal.^{2,4,21} Unfortunately most patients are extremely deficient prior to the appearance of clinical and physical symptoms;²¹ hence laboratory testing can be done prophylactically. The usual dose of selenium in PN is 20-60 mcg/day; however consensus is that needs are actually increased to 60-100 mcg/day.^{3,9} Selenium requirements are elevated in malabsorptive states⁹ and increased dosage is controversial in critically ill, septic, and burn patients.³ Although rare,²² selenium toxicity is likely to appear when levels are tenfold higher than normal.²¹ Toxicity may cause oxidative cell and tissue death. Symptoms may include hair loss, brittle nails,²¹ skin changes, decay of teeth, and neurogenic abnormalities.¹⁰ Selenium laboratory studies lack correlation to actual selenium storage and likely reflect acute changes between tissues.⁹ Some professionals feel that erythrocyte glutathione peroxidase activity could be more reflective of selenium storage however; further studies are warranted.^{9,11}

Zinc

Zinc is a metalloenzyme that has roles in immune function, stress response, wound healing, and glucose control. As a cofactor, zinc also aids in the metabolism of macronutrients. Transported by plasma protein and albumin, >85% is stored in the skeletal muscle and smaller amounts in the bone, skin, liver, pancreas, kidney, and prostate.^{23,24} Zinc deficiency can appear rapidly, within 14 days to 3 months of supplementation holiday,^{23,24} and is often related to prolonged severe malnutrition, high enteric losses, and/or thiazide diuretic use.¹⁰ Deficiency characteristics are detectable once levels are severely low, often present with physical signs: acrodermatitis enteropathica, alopecia, hair pigmentation changes, stomatitis, glossitis, perioral

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Table 3. Detecting Trace Element Deficiency and Toxicity

	Element	Chromium	Copper
Trace Element Deficiency	Patients of Higher Risk	Elderly, athletes, pregnant women, ²⁶ long term PN without chromium supplementation ¹⁰	Short bowel syndrome, high GI losses, post-gastrectomy, small bowel resection or gastric bypass surgery, ¹³ burns, on large doses of oral Zn, regular antacid use, Menkes disease ¹⁰
	Physical Signs & Symptoms		Foot numbness, gait difficulty, ^{4,13} hair hypopigmentation, kinky hair, general weakness ²⁴
	Clinical Signs & Symptoms	Glucose intolerance, hyperlipidemia, neuropathy, rare encephalopathy ^{8,9,10}	Leukopenia, hypochromic and normocytic or microcytic anemia ^{2,10}
Trace Element Toxicity	Patients at Higher Risk	(not well documented) Poor renal function ⁸	Cholestasis, hepatic failure ¹⁶
	Physical Signs & Symptoms	Neuropathy ²⁶	Metallic taste, jaundice ²⁶
	Clinical Signs & Symptoms		Nausea, vomiting, epigastric pain, headache, dizziness, weakness, diarrhea, tachycardia, hypertension ²⁶ elevated alkaline phosphatase, ALT, AST, & bilirubin Note: copper should not be empirically removed from PN unless serum level checked and it is found to be high. If removed, put in place monitoring schedule to reevaluate periodically to avoid creating a deficiency state.

Manganese	Selenium	Zinc
(not well detected) weight loss, transient dermatitis ¹⁰	Long-term PN dependence, cystic fibrosis, alcoholism, burns ¹⁰	Severely malnourished, high GI losses, thiazide diuretic users ¹⁰
(not well detected)	Whitened nail beds, hair and skin pigmentation loss, muscle tenderness, ^{2, 21} under-development	Dermatitis, alopecia, dull/lackluster hair, stomatitis, glossitis, perioral ulcers, periungual lesions, ^{10, 23} poor wound healing, under-development, dysgeusia, hypogeusia, poor night vision ¹⁰
Cholestasis, hepatic failure	Cardiomyopathy, skeletal muscle myopathy, macrocytic anemia, Keshan Disease ^{2, 10, 21}	Anorexia, delayed sexual maturation, poor immunity ¹⁰
Parkinson's like signs and symptoms ¹⁰	Hair loss, brittle nails, ²¹ skin changes, tooth decay, ¹⁰ garlic breath odor, metallic taste ²⁶	Nausea, dizziness ¹⁰
Iron deficiency anemia, hallucinations ^{10, 26} , elevated alkaline phosphatase, AST, ALT, and bilirubin Note: manganese should not be empirically removed from PN unless serum level checked and it is found to be high. If removed, put in place monitoring schedule to reevaluate periodically to avoid creating a deficiency state.	Neurogenic abnormalities, ¹⁰ mood changes ²⁶	Impaired neutrophil & lymphocyte function, ² copper deficiency, ¹⁰ urinary tract infection ²⁵

ulcers, and periungual lesions.^{23,24} Clinical symptoms often entail delayed wound healing, delayed sexual maturation, reduction of taste sensitivity, poor night vision and impaired immunity.¹⁰ Standard dosage administered through PN is 2.5-5 mg/day. Patient with high GI loss may require 12-17 mg/liter lost,^{3,24} with a proposed upper limit of 50 mg/day.¹⁰ Some clinicians proactively supplement 10 mg/day for patients at high risk for deficiency.¹⁰ ASPEN does not have an adjustment they would like to make at this time; however, per Shike et al. average zinc dose given was 7.6 mg/day to maintain adequate zinc status, adequate for 90% of the patient population.¹² They supplemented 6.7 mg/day versus 9 mg/day in their non-short bowel as opposed to short bowel patients.¹² Rare toxicities have been detected, often expressed as dysfunction of neutrophils and lymphocytes² and have been associated with urinary tract infections.²⁵ Zinc laboratory studies have questionable accuracy as zinc is tightly regulated and reserved in the blood until supply is scarce; hence zinc deficiency may be caught late.⁹

SUMMARY

Trace elements are essential in providing adequate PN formulations in long-term PN patients. Though infused in minute quantities, trace elements have a significant role in health and well being. However, if not carefully monitored in these patients, they can have detrimental effects. It is vital that clinicians who care for these patients understand dosages available, patients' conditional requirements, anticipate where potential toxicities and deficiencies might occur and the importance of dosage adjustment as appropriate. As most laboratory measures are unsatisfactory, assessment of the entire clinical picture is critical in determining the best plan of care. Develop a plan for scheduled monitoring, and if faced with product shortage, see the ASPEN website for suggestions: http://www.nutritioncare.org/news/parenteral_nutrition_trace_element_product_shortage_considerations ■

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