TABLE I. Commercially Available Chromium Preparations

Product	Manufacturer	Type of Salt	Ionic Conc. (mg/ml)	Container
Chrome Trace™	Armour	Chloride	.004	10 ml vials
Chromic Chloride, USP	LyphoMed	Chloride	.004	10 ml vials
Chromic Chloride, USP	LyphoMed	Chloride	.004	30 ml MDV
Chromic Chloride, USP	LyphoMed	Chloride	.02	10 ml vials (concentrate)

chromium deficiency have been reported in patients undergoing TPN. Features intrinsic to parenteral nutrient infusion promote chromium excretion. It is prudent, therefore, to include chromium in TPN regimens projected to extend over periods of months.

B. Chemistry

Chromium has an atomic number 24, and an atomic weight of 51.996. It exists chiefly as Cr(II), Cr(III) and Cr(VI). The hexavalent (chromate) compounds are unable to be utilized biologically, and are toxic when taken parenterally. The chromic, Cr(III) form is of major biological importance as a nutrient. The chromic ion has a tendency to bind to anions and, under certain conditions of pH and ionic strength, undergoes olation with water to form polymers.

C. Dosage Forms/Concentrations/Manufacturers

The expert panel of the AMA[4] specified a recommended ionic concentration for chromium of 4 ug/ml. The recommended source is chromic chloride ($CrCl_3 \cdot 6H_2O$, mol wt 266.45), containing 19.5% Cr(III). Thus, the concentration of the chloride salt would be 20.5 ug/ml to meet these specifications (see Table I).

D. Uses/Functions

Chromium is an essential nutrient with a relatively rapid turnover.[5] The

Chapter 11

CHROMIUM

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I. Product Information

A. Introduction

Chromium participates in metabolism as a component of a small, organic entity known as glucose tolerance factor or GTF.[1] The exact chemical nature of this entity is not known precisely, but it is known to contain trivalent chromium in association with amino acids. GTF is believed to potentiate the action of insulin at the cellular level, participating in the transmission of the hormonal message to the receptor cell. Chromium is an essential trace mineral, and its deficiency leads to impaired glucose tolerance of a pseudodiabetic nature. Chromium is not stored well by the body, and normal aging is associated with a "physiological" depletion of the mineral.[2] Recent evidence also suggests a role for chromium in lipoprotein metabolism.[3] At least two well-documented cases of

En: *Clinical Guide to Parenteral Micronutrition*. First Edition. T.G. Baumgartner (Ed.). Chicago, Lymphomed Inc. 1984 p.137-144

response to glucose mobilizes chromium, and it is filtered by the kidneys during this passage into the circulation.[6] TPN represents a large, direct influx of glucose into the bloodstream, and requires an enhanced pancreatic insulin response. Whether continuous (e.g. hospital) or discontinuous (e.g. home) patterns of TPN delivery would be more provocative of chromium diuresis is not known. Glucose tolerance, the metabolic adaptation to the very unnatural delivery of carbohydrates by parenteral infusion, must be maintained during TPN and "diabetic-like" damage to peripheral organs is to be avoided. Moreover, as energy storage is a legitimate aim of acute repletion regimens of TPN, insulin must function at the cell membranes to facilitate the uptake of glucose into cells, to the extent that chromium and glucose-tolerance-factor participate in this process; maintenance levels of exogenous chromium in daily parenteral infusions are advisable. A more speculative, but equally legitimate concern, is the role that chromium may play in lipid metabolism. TPN regimens are now becoming lifelong in many patients; the upper limits of longevity on exclusive parenteral nutrition are being probed and pushed back by the patients who have now been maintained for over a decade at certain pioneer institutions. To the extent that chromium may be hypocholesterolemic, or that chromium nutriture may be a true risk factor in development of ischemic coronary disease,[7] the long-term consequences of insufficient intravenous chromium administration may go beyond carbohydrate intolerance to the morbidity associated with atherosclerosis. (It would be unfortunate if the definitive, prospective data for a firm association with chromium status and heart disease were derived from long-term TPN patients.)

II. Professional Implications

A. Preparation/Compounding/Analysis/Synthesis

Ultrapure forms of chromium chloride are available for easy formulation of additive solutions. The analysis of the solution is hampered, however, by the difficulties inherent in the determination of chromium concentrations by atomic absorption spectrophotometry.[8] Neutron activation analysis is probably the analytical method of choice, but it requires a nuclear reactor facility.

B. Antagonists/Inhibitors/Potentiators/Synergistic Agents

Free, ionic iron is a potential antagonist since it might saturate the binding sites on transferrin, which is also the transport protein for chromium. For chromium to function in metabolism, insulin must be available; in the totally insulinopenic state, no amount of chromium will improve glucose tolerance.

C. Contraindications/Precautions/Warnings

There are no contraindications to the routine maintenance or therapeutic dosing of patients on TPN with chromium. Supplementation of chromium to a deficient patient might substantially decrease his or her insulin requirement, and careful monitoring of blood sugar is required during the early period of chromium addition to avoid hypoglycemia. Reduction or elimination of exogenous insulin might be possible as chromium nutriture is restored.

D. Pharmacokinetics/Disposition

1. Bioavailability/Absorption

Problems with the absorption of dietary chromium are manifold, but parenterally administered chromium bypasses this barrier. As chromium is thought to act as part of a small organic molecule (GTF), the efficient utilization of inorganic chromium supplements may depend on the rate or efficiency of conversion to GTF. The bioavailability of chromic chloride is theoretically less than that for preformed GTF. A rapid response to chromium administration was seen in the two reported cases of TPN-induced chromium deficiency.[9, 10]

2. Distribution/Binding

The total-body content of chromium is estimated to be 6 to 10 mg. It is fairly uniformly distributed, with tissue concentrations ranging from 0.02 to 2.0 ug/g. Approximately 1 mg of chromium is found in a transport form in the circulation, bound to transferrin. Chromium also enters the circulation – presumably as GTF – in response to carbohydrate meals.

3. Blood Levels

It is currently accepted that normal circulating levels of chromium range from 0.038 to 0.352 ug/L (mean 0.160 ug/L).[11]

4. Metabolism

The organic complex of chromium–GTF–participates in the action of insulin at the tissue level. During interprandial periods, GTF chromium is stored in a storage pool; the precise anatomical location is undetermined. Following a meal, and in association with pancreatic secretion of insulin, GTF levels rise in the circulation, only to decline several hours after the meal. Theoretically, continuous infusion of glucose solutions (as in in-hospital TPN) would provoke a continuous mobilization of GTF into the blood stream.

5. Excretion

Oral chromium is poorly absorbed from the diet. Endogenous chromium is

TABLE II. Laboratory and Diagnostic Options for Assessing Human Chromium Status

Circulating (plasma/serum) chromium concentration
Hair chromium content
Glucose tolerance/insulin requirement changes
Urinary chromium excretion after glucose load
Circulating chromium concentration change after glucose load

excreted primarily in the urine. Normal urinary concentrations of chromium are 0.2 to 0.6 ug/L. The (active) GTF chromium is more filterable than the transferrin-bound (transport) chromium, and chromium is excreted by the kidneys in a cyclical fashion, following mealtime stimulation of GTF mobilization.

III. Patient Considerations

A. Administration

Chromium additives should be administered by diluting the assigned dosage into the TPN infusion solution. It can be added individually, or as part of a multi-element preparation subject to the consideration previously discussed. If specifically increased requirements for chromium are detected, an additional amount of the mineral above that provided by multi-element additives will be required.

B. Adverse Reactions

None known.

C. Monitoring

The laboratory and diagnostic options for determining chromium nutriture are listed in Table II. Assessing chromium status is difficult for several reasons; none of the indices listed in the table is necessarily a faithful indicator of chromium status, and the analytical determination of the chromium in biological materials is not widely available, and is fraught

with pitfalls and limitations. The circumstances of treatment with TPN simulate the provocative tests for chromium mobilization, confounding their use in these patients. Early detection of chromium deficiency, therefore, is problematic in TPN patients, and the most reliable guidance is provided by clinical observation (such as the development of or the change in the insulin requirement of a patient). The response to formal glucose tolerance tests or the change in insulin requirement after a course of chromium supplementation could be used to provide a retrospective diagnosis of an initially chromium-depleted status.

D. Expiration

The expiration date on the commercially available product will provide the expected shelf-life of chromium trace element. Single use vials should be discarded within 24 hours in spite of the preservative action of certain trace elements. TPN solutions containing chromium trace element may be stored for up to 24 hours unless otherwise determined. It should be remembered that Maillard reaction products have been shown to chelate trace elements.[12]

E. Storage

Most trace mineral additives do not contain bacteriostatic agents. They must be discarded within 24 hours after a single use if stored in a laminar flow environment.

F. Requirements/Deficiencies

The AMA expert committee[4] has established a recommendation for daily parenteral requirements for chromium (see Appendix A, General Tables). For pediatric patients, infusion of 0.14 to 0.2 ug/kg will meet the needs for maintenance and growth. Maintenance requirements for stable adults are 10 to 15 ug daily. No adjustments were made for catabolic states or excessive intestinal fluid loses. Two well-documented cases of TPN-associated chromium deficiency have been reported.[9,10] Jeejeebhoy et al.[9] described a 34-year-old woman who began to lose weight and manifest glucose intolerance tha trequired insulin coverage after 39 months of a course of TPN, She developed a peripheral neuropathy. Low levels of hair and blood chromium prompted the institution of intravenous chromium replacement. The case report by Freund et al.[10] was similar, except that the glucose intolerance occurred at 5 months, and the neurological manifestation was metabolic encephalopathy. Chromium administration to both patients brought glucose metabolism under control without the need for exogenous insulin, resolved the neurological manifestations, and allowed

TABLE III. Clinical Manifestations and Consequences of Chromium Deficiency

Glucose intolerance
Excessive insulin requirement
Peripheral neuropathy
Metabolic-encephalopathy
Hyperlipidemia
Increased susceptibility to cardiovascular disease (?)

weight gain and stabilization on 2000 kcal of energy intake daily. The clinical consequences of chromium deficiency are shown in Table III.

G. Dose (Treatment/Toxicity)

Therapeutic dosages of chromium in these patients were 250 and 150 ug daily, respectively; clinical responses were noted when a total dose of 3100 and 9000 ug of chromium had been administered to the respective patients. No specific manifestations of chromium toxicity are anticipated from parenteral administration. It should be noted, however, that European intravenous solutions for TPN have elevated levels of chromium due to contamination by contact with stainless steel during processing;[13] short-term TPN therapy resulted in progressive increments in circulating chromium concentrations.

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