

For more information on minerals see *Laboratory Evaluations in Molecular Medicine, Nutrients, Toxicants and Cell Regulators*, Chapter Three - "Minerals"

Measuring concentrations of elements in erythrocytes provides a look at how well cellular levels are maintained because erythrocyte mineral levels reflect mineral status over a period of 4 months (the life cycle of an erythrocyte). Other specimens, like urine or plasma, are affected by daily dietary fluctuations.

In the process of their formation in bone marrow, erythrocytes acquire nutrient elements like zinc according to the availability of each element. The same may be said for the toxic elements, which means that high levels of these raise suspicion of chronic tissue penetration due to toxic exposure and inadequate detoxification mechanisms. All of the essential trace elements are dependent on stomach acid production for intestinal absorption.

#	Name		Metabolic Association	Potential Intervention
Nutrient Elements				
1	Calcium	Ca	Myriad cell regulatory effects	See Calcium section
2	Chromium	Cr	Insulin target cell binding	200 - 400 µg/d
3	Copper	Cu	Detox pathways	3 - 4 mg/d
4	Magnesium	Mg	ATP energy transfer	200 - 400 mg/d
5	Manganese	Mn	Biosynthetic pathways	5 - 15 mg/d
6	Potassium	K	Neuromuscular function	Fresh fruits & vegetables
7	Selenium	Se	Antioxidant protection	200 - 1000 µg/d
8	Vanadium	V	Cholesterol, triglycerides	200 - 1000 µg/d
9	Zinc	Zn	Cofactor for numerous enzymes	15 - 60 mg/d
Toxic Elements				
			Accumulation Site	
11	Aluminum	Al	Lung	Avoidance
12	Arsenic	As	Skin, Bladder, Lung	
13	Cadmium	Cd	Kidney	Zinc
14	Lead	Pb	Bone	Calcium
15	Mercury	Hg	CNS/Brain	Selenium
<i>The numbers in the left-hand column in the table correspond to those on the laboratory report of minerals in erythrocytes.</i>				

Calcium (Ca)

Erythrocyte calcium is associated with the etiology of heart disease and stroke, as shown by erythrocyte morphological changes in ischemic vascular disease. Intracellular calcium content plays an important role in the induction of blood pressure elevation. Total erythrocyte calcium is elevated in hypertension and in postnatal hypoxic ischemic encephalopathy. Calcium levels in erythrocytes are not an accurate measure of calcium nutritional status because of the strong mechanisms maintaining the critical intracellular calcium concentrations independent of the total body calcium regulation exerted by parathyroid hormone, vitamin D, and other regulatory molecules.

Chromium (Cr)

Chromium accumulates primarily in spleen and heart tissue. Dietary sources include liver, brewer's yeast, nuts, and whole grains. The greatest number of chromium studies involve its role in glucose metabolism. Sugar metabolism was improved in over 80% of individuals with a slight glucose intolerance by using 200 mcg/d chromium supplement. Chromium used in this way affects only those who are deficient in chromium. This nutrient impacts sugar metabolism through its role in uptake of

insulin, and losses of chromium in urine are related to increased mobilization in response to the stimulus of frequent blood sugar peaks. Chromium also aids in lowering LDL cholesterol and raising HDL cholesterol.

Copper (Cu)

Most copper is concentrated in liver, brain, and hair but is present in all other tissue. Best dietary sources are whole grains, nuts, seeds, beans, liver, and shellfish. Most of the copper present in erythrocytes is bound to the enzyme superoxide dismutase (SOD), which protects the cells from oxidative damage. Dietary deficiency of copper is seen as low levels of erythrocyte copper and SOD, even in early stages of copper depletion. Impairment of function due to copper deficiency may result from reduced activities of the enzymes, ceruloplasmin, monoamine oxidase, lysyl oxidase in connective tissue, and SOD. Loss of these biochemical functions can lead to anemia, neural degeneration, lung and bone problems, CVD, and accelerated aging. In copper deficiencies, supplementation with 3-5 mg/d copper aspartate is helpful. Chronically elevated plasma copper may result in elevation of erythrocyte copper levels as well, although the two specimens represent different copper utilization. About 80% of erythrocyte copper is associated with SOD, while

most plasma copper is bound to ceruloplasmin. Patients with Wilson's disease, an inherited copper accumulating disease, show elevated erythrocyte copper resistant to copper-lowering treatments. In these cases, copper accumulates in liver and brain where it causes tissue degeneration, apparently due to the stimulation of protein and oxidative DNA damage.

Magnesium (Mg)

Magnesium serves as a cofactor in approximately three hundred enzyme systems, making this element a critically important nutrient for many bodily functions. Deficiency conditions can cause a wide variety of problems including hypertension, diabetes, and the pre-menstrual syndrome. Magnesium plays a vital role in normal cardiac function, and deficiency has been increasingly associated with cardiovascular disease. Some suggest hypomagnesemia is in itself atherogenic, and low magnesium levels in drinking water have been associated with increased risk of myocardial infarction. Magnesium has also been found to be useful in the treatment of congestive heart failure, tachycardia, and other arrhythmias. Magnesium deficiency in humans is rarely severe, although symptoms of marginal deficiency may be many and varied. Symptoms frequently associated with magnesium deficiency in humans are neuromuscular tremors, fasciculations, and gross muscle spasms. The magnesium content of red blood cells is a good indicator of short-term magnesium status and low levels indicate nutritional deficiency. Because of the requirement for magnesium by many enzymes involved in energy transfer, magnesium deficiency affects all tissues. As the largest energy user, nervous tissue shows the earliest signs of deficiency, with the appearance of dullness and listlessness, nausea and loss of appetite, alopecia (rapid hair loss), tremors, and convulsions. The major dietary sources of magnesium are nuts, beans, and dark green vegetables.

Manganese (Mn)

Manganese, like magnesium and zinc, is associated with a large number of enzymes in many areas of metabolism, especially those involved in connective tissue maintenance, fatty acid synthesis, and Krebs cycle pathways. Manganese deficiency contributes to glucose intolerance. Its absorption in the intestine is impaired by calcium, phosphate, and iron. Manganese is found in fruits, whole grains, and leafy green vegetables.

Potassium (K)

Erythrocyte potassium is the best single measure of body potassium status. Mild to moderate potassium deficiency is frequently found in those whose diet is low in fresh vegetables and fruit, especially if meat and fish intake is also low. Fortunately, the body has strong conservation mechanisms that dampen the effects of periods of low intake. Nervous and muscle tissues have strong requirements for potassium to maintain excitability. Depletion of body potassium can lead to a wide range of effects, including hypertension, heart arrhythmias, and muscle weakness. The use of vegetable juices, citrus juices, bananas, melons, and other fruits and vegetables will increase potassium levels.

Selenium (Se)

Selenium has a fairly narrow window of safe effectiveness and works closely with vitamin E. Protein-containing foods in which the selenium is bound to amino acids, such as meats and seafood, are good sources of selenium. Evidence shows that dietary intake of selenium is directly related to levels of selenium in erythrocytes. Low levels indicate depleted selenium pools. Selenium functions primarily as an activator of enzymes necessary for cellular protection from oxidative damage and maintenance of normal redox potentials. A primary role of selenium in erythrocytes appears to be the activation of the enzyme glutathione peroxidase, whereby glutathione (a critical antioxidant and antitoxin for all cells) reacts with oxygen radicals. Similarly, selenium catalyzes glutathione reductase, an enzyme that keeps glutathione in its reduced or active form.

Vanadium (V)

Recent data show vanadium to be essential for humans. Food concentrations vary greatly. Diets high in unsaturated oils have more vanadium than those high in saturated oils. Food is generally low in vanadium. Absorption of vanadium is highly dependent on its form. It is retained by liver and bone and transported on the blood protein transferrin. Vanadium lowers cholesterol synthesis and may lower plasma triglycerides in humans. It promotes mineralization of bones and teeth and may protect against caries. Vanadium levels can become high due to environmental exposure to chemicals containing this element, as it is absorbed through inhalation.

Zinc (Zn)

Sources of zinc in the diet include whole grains, nuts, seeds, and seafoods, especially shellfish. Growth and repair of any tissue is dependent on zinc as an activating cofactor for DNA/RNA polymerase. For this reason, zinc is vital to the normal healing of wounds and skin disorders. Dermatoses related to low zinc status are well-known; acrodermatitis enteropathica is a severe deficiency seen in infants, and a milder form is seen in adults. Zinc is required for normal immune function. In fact, there are many similarities between the immunologic affects of zinc deficiency and those of AIDS. Low zinc is associated with low T-helper lymphocytes. If intake of calcium, copper, or iron is excessive, tissue zinc may become depleted. If zinc is elevated, problems that might occur include iron nonresponsive anemia due to related copper deficiency and increased vascular disease risk from lowered HDL cholesterol.

Toxic Metals

Toxic metals may exchange between blood plasma and erythrocytes after a person is exposed. The concentration of these metals in erythrocytes also is determined by the content of the tissue where erythrocytes originate: the bone marrow. The marrow exchanges the metals with the mineral matrix of bone. Thus, elevated erythrocyte levels of a toxic metal may reflect a deep tissue accumulation of the element.

The distribution of elements between bone and various soft tissues varies with each element. For example, lead tends to preferentially deposit in bone, while cadmium concentrations are usually highest in kidney. No single tissue or body fluid provides the whole answer to total body toxic metal load.

The question of why a patient has developed a high toxic metal load is frequently difficult to answer. Obvious sources of high exposure from industrial occupations where heavy metals are used are easily identified, but chronic low-level exposures can escape notice.

Aluminum (Al)

The best-known toxic effects of aluminum are dialysis encephalopathy and dementia in uremic patients. These cases have provided valuable insight about other toxic effects of aluminum, including impaired memory, dementia, aphasia, ataxia, convulsions, and characteristic EEG changes. Urine is the major elimination route of aluminum, so once a chelating agent has mobilized and bound the element, it is relatively easily eliminated. Potential sources include antiperspirants, soda cans, baking soda, and toothpaste.

Arsenic (As)

Significant human exposure to arsenic results from the ubiquitous distribution of trivalent and pentavalent forms of inorganic arsenic in nature. In addition to the human hazard associated with neoplastic outcomes discussed below, recent evidence links arsenic exposure and risk to vascular disease related to atherosclerosis. Long-term arsenic exposure in drinking water shows a dose-response relationship to carotid atherosclerosis. The mechanism involves the induction of expression of genes coding inflammatory mediators.

Inhaled arsenic has long been known to cause lung cancer. Ingested arsenic has also been linked to cancers of the skin, bladder, and lung. Some areas of California and Nevada contain roughly 50-100 ug/liter of arsenic (the highest level of arsenic found in major water supplies in the US). At the other end of the spectrum are water supplies containing less than 10 ug/liter. The current drinking water standard for arsenic in the U.S. and much of the world is 50 ug/L. The WHO has recommended lowering permissible concentrations to 10 ug/L, and the U.S. EPA to 2 ug/L. Linear risk extrapolation to lifetime consumption of water with an arsenic concentration of 50 ug/L results in cancer mortality risk estimates of around 1 in 100 adult deaths being attributable to arsenic, mainly as a consequence of lung and bladder cancer. Dietary arsenic is contributed by various foods including cereals and breads, 18.1%; starchy vegetables, 14.9%; and meats and fish, 32.1% of total average daily intake.

Human tissues contain arsenic detoxification proteins called aquaporins. Different levels of expression of aquaporins may account for differences in arsenic toxicity among individuals. Paradoxically, arsenite is an effective cancer chemotherapeutic agent. Its anhydrous form, arsenic trioxide (Trisenox) has been approved as a chemotherapeutic agent for the treatment of acute promyelocytic leukemia. Differences in expression of aquaporins could lead to variability in response to drug therapy in different patients.

Cadmium (Cd)

The fact that cadmium is bound by the abundant zinc-sequestering protein, metallothionein, and that this protein occurs in high concentration in kidney makes cadmium one of the most easily removed toxic elements. During chronic exposure, the kidney contains a major part of the body burden of cadmium. Any intervention that increases the passage of metal chelating agents through the kidney will lower total body burden of cadmium. Cadmium toxicity impacts the kidney, where damage to proximal tubules has been described. Also, cadmium compounds are classified as carcinogenic to humans. Potential sources include drinking water, processed foods, cigarette smoke, paint pigments, and silver polish.

Lead (Pb)

Lead toxicity causes paralysis and pain in the extremities due to effects on demyelination, axonal degeneration, and presynaptic block. Normocytic, sideroblastic anemia is the consequence of lead's inhibiting effects on enzymes in the heme biosynthesis pathway. Other clinical signs associated with lead toxicity are kidney damage, epigastric pain and nausea, and male and female reproductive failure.

Lead toxicity commonly affects sensory, visual, auditory, and cerebellar (coordination) functions, reflecting the nervous system impact of this element. Patients may have paraesthesia in the region around the mouth and in the hands immediately after exposure.

Various intravenous chelation agents, including penicillamine and EDTA, have been shown to be effective in reducing lead body burden. Increased dietary calcium helps lower the intestinal absorption of lead. Potential sources of lead include leaded house paint, drinking water from lead plumbing, pesticides, and newsprint.

Mercury (Hg)

Conditions ranging from childhood autism to adult neurological dysfunction and dementia can result from the toxic effects of mercury. Mercury tends to form very stable bonds with various amino acid side chains of proteins, making it difficult to remove quickly. The major part of mercury in blood is bound to hemoglobin in red cells.

Sulfur-containing agents, such as dimercaptosuccinic acid (DMSA), are the more effective agents for removing mercury from tissues. The most important protective agent is dietary selenium, which helps reduce the toxic effects of mercury. Potential sources include dental amalgams, broken thermometers, cosmetics, and predator or fresh water fish.