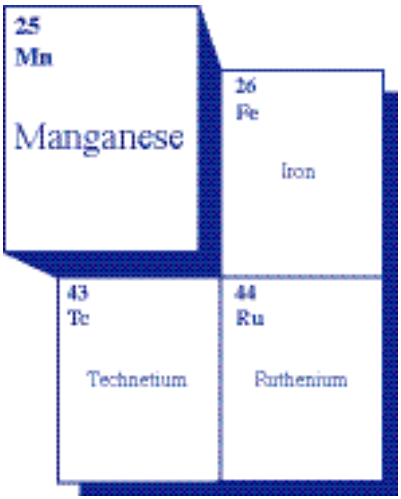

Manganese

Introduction

Manganese is considered to be a trace mineral, of which the average adult needs 2-5 mg per day to meet the Estimated Safe and Adequate Daily Dietary Intake (ESADDI).[1] Americans, however, especially women, consume less than these levels.[2] Even at 2-5 mg per day, women can be in negative manganese balance, with the daily excretion of manganese exceeding intake.[3]

Manganese is necessary for the production of manganese superoxide dismutase, an antioxidant enzyme that quenches the superoxide radical. Many environmental and dietary factors, including ozone,[4] alcohol,[5] high polyunsaturated fat diet, and oxidative stress[6] increase the need for superoxide dismutase and may increase the biological need for manganese.

Biochemistry and Mechanisms of Action

Manganese concentrates in mitochondrial tissue and in the bone, liver, pancreas, and kidney.[7] Manganese is an essential component of carbohydrate metabolism, reproductive function, and skeletal and cartilage development.[8] Manganese is the critical element in the metalloenzymes pyruvate decarboxylase and superoxide dismutase that are involved in energy production and immune function. Manganese also activates phosphatases, kinases, decarboxylases, and glycosyltransferases, facilitating the synthesis of protein and DNA in the production of mucopolysaccharides found in cartilage.[3] Superoxide dismutase – an enzyme that protects cell membranes from lipid peroxidation,[9] radiation- or chemical-induced carcinogenesis,[10] reperfusion injury,[11] and inflammation[12] – has been found at low levels in manganese deficiency.[13] In animal studies, manganese supplementation has significantly elevated levels of superoxide dismutase.[13]

Pharmacokinetics

Manganese is absorbed in the small intestine, but absorptive efficiency is poor. Absorbed manganese is very quickly secreted (within minutes) into the gut in bile. It is estimated that six percent of ingested manganese is absorbed.[14] This low absorption and rapid elimination serves as a protective mechanism against manganese toxicity.[15] Absorbed manganese is transported in the blood bound to plasma carrier proteins and is eliminated primarily through the feces.

Deficiency States

Human manganese deficiency is uncommon. Severely manganese-deficient animals exhibit symptoms of growth retardation, dermatitis, and reproductive failure, as well as metabolic changes including reduced HDL cholesterol and diabetic-like glucose intolerance.[16,17] Decreased serum manganese has been found in epileptics,[18-20] diabetics,[21,22] and persons with osteoporosis.[23]

The case of a well-known basketball player who had a history of recurrent non-healing fracture, bone pain, and no measurable blood manganese was brought to the attention of researchers at the University of California at San Diego.[24] The reversal of this condition with supplemental manganese, calcium, zinc, and copper initiated more research in the area of manganese metabolism and bone physiology. Other patients with slow fracture-healing rates were also shown to have low blood manganese, copper, and zinc levels.[24]

Clinical Indications

Osteopenia/Osteoporosis

Multiple studies in animals have shown manganese-deficient diets in rats prevent cartilage formation and produce osteopenia, the result of an imbalance between osteoblastic and osteoclastic activity.[25] In controlled studies of postmenopausal women with and without bone density changes, the serum manganese levels in the osteoporotic women were significantly lower.[23] In a randomized, controlled, two-year trial, the same researchers used a trace mineral combination of 15 mg zinc, 2.5 mg copper, and 5 mg manganese with calcium citrate-malate (1,000 mg elemental calcium) against placebo and calcium citrate-malate alone in postmenopausal women.[23] The increase in bone gain was greatest in those given trace minerals plus calcium, although the change did not reach statistical significance. Although this trial was unable to look at the effect of single element supplementation, evidence for a synergistic effect exists. Supplementation with manganese appears to be warranted in those at risk for osteoporosis, particularly if manganese levels are low.

Epilepsy

Several studies have found low levels of manganese in blood or hair of epileptic adults and children.[18-20] In one study of 52 epileptics, the difference between manganese levels was significant; blood manganese levels in epileptics were 24-percent lower than control levels ($p<0.002$).[18] In those with significantly lower manganese, the frequency of seizure activity and cases of non-trauma-related epilepsy were positively correlated with depressed manganese levels. One case study of pediatric seizure disorder involved a boy with blood manganese levels of 50 percent of normal values.[26] After supplementation of 20 mg per day, seizure frequency decreased and speech, gait, and cognitive function improved.

Diabetes

Levels of both erythrocyte and lymphocyte manganese levels have been shown to be significantly depressed in type 1 diabetics.[21,22] Manganese has been shown to have hypoglycemic effects in type 1. A case report of a 21-year-old male with type 1 diabetes revealed consistent depressions in blood glucose levels, even with hypoglycemic events, after 3-5 mg oral manganese chloride supplementation.[27] Manganese deficiency, in addition to a role in inhibiting gluconeogenesis and altering carbohydrate metabolism,[28] appears to play a role in the pathology of diabetes through decreased levels of the antioxidant enzyme manganese superoxide dismutase.[29] In animal studies, manganese-deficient diets in diabetic rats decreased the production of manganese superoxide dismutase in the kidney and liver, and increased lipid peroxidation. Increased oxidative damage is linked to nephropathy in animal models of diabetes and possibly vascular and neural complications in human diabetes.[30] In young, female non-diabetics 15 mg manganese had a significant elevating effect on lymphocyte manganese superoxide dismutase.[31]

Side Effects and Toxicity

Manganese balance studies reveal some people can be in positive balance with intakes of 2.5-15 mg per day, while others may be in negative manganese balance at the same level of dietary intake. This wide variance in need for manganese may be related to factors that inhibit manganese absorption: dietary calcium, iron, phosphorus, and phytate.[15] Another difficulty in understanding manganese nutrition is that in rats, at least 37 percent of absorbed manganese is excreted in bile.[32] Studies showing greater levels of biliary manganese excreted with concomitant heavy metal administration may indicate a relationship between manganese loss and heavy metal accumulation and elimination.[33,34]

There is only one published case of "supplemental manganese" toxicity in the literature in an elderly man who had been taking unknown amounts of manganese for several years.[35] He had significantly elevated serum manganese levels, symptoms of dementia, and a Parkinson-like syndrome.

Elevated plasma manganese levels have been documented in parenteral manganese supplementation and in patients with impaired liver function or biliary secretion. Manganese toxicity has been documented in chronic inhalation in manganese miners and arc welders. Toxicity symptoms include anorexia, growth depression, aggressive behavior, reproductive failure, anemia, severe psychiatric disorders, and neurological disorders resembling schizophrenia and Parkinson's disease.[36]

Manganese is considered non-toxic when administered orally. Research on oral manganese has shown the body is protected from oral toxicity by low absorption levels and a high rate of elimination by the liver.[15] In several small studies, elevated hair manganese levels have been suspected to contribute to aggressive behavior,[37] attention deficit disorder,[38] dementia,[39] and

learning disorders.[40,41] It is unclear whether these correlations hold merit, but some practitioners have opted to use caution with supplemental manganese.

Dosage

Case studies cited above used 5-20 mg doses for treatment of manganese deficiency. The Tolerable Upper Intake Level (the highest level of daily nutrient intake likely to pose no risk of adverse health effect in almost all individuals) is 11 mg daily.[42]

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