INE INSTITUTE OF NUTRITIONAL ENDOCRINOLOGY

Micronutrients: Manganese

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General Info

- ✓ Needed in small quantities
- ✓ Both nutritionally essential and potentially toxic
- ✓ From the Greek word for "magic"
- ✓ Scientists are still working to understand the diverse effects of manganese deficiency and manganese toxicity

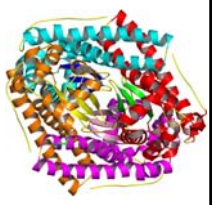
Manganese Functions

- ✓ Antioxidant
- ✓ Metabolism (as an enzyme co-factor)
- ✓ Bone development
- ✓ Wound healing
- ✓ Connective tissue
- ✓ Blood clotting factors
- ✓ Sex hormones synthesis
- ✓ Fat and carbohydrate metabolism
- ✓ Calcium absorption
- ✓ Blood sugar regulation
- ✓ Brain and nerve function

Manganese as an Antioxidant

Manganese superoxide dismutase (MnSOD)

- ✓ Principal antioxidant enzyme in the mitochondria
- ✓ Catalyzes the conversion of superoxide radicals to hydrogen peroxide (H_2O_2)
- ✓ (H_2O_2) is reduced to water by other antioxidant enzymes
- ✓ Superoxide radical is one of the reactive oxygen species produced in mitochondria during ATP synthesis

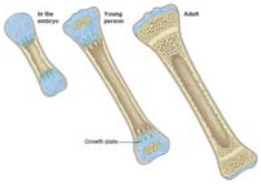


Manganese Dependent Enzymes

- ✓ **Pyruvate carboxylase and Phosphoenolpyruvate carboxykinase (PEPCK):** Gluconeogenesis
- ✓ **Arginase:** Urea cycle in liver for detoxification of ammonia generated during amino acid metabolism
- ✓ **Glutamine synthetase:** Converts glutamate to glutamine in brain

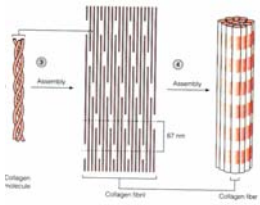
Bone Development

- ✓ Manganese is the preferred cofactor of enzymes called **glycosyltransferases,** required for the synthesis of proteoglycans that are needed for the formation of healthy cartilage and bone
- ✓ **Glycosyltransferases** are enzymes that catalyze the transfer of saccharides from nucleotide sugars resulting in the formation of a carbohydrate, glycoside, oligosaccharide, or a polysaccharide



Wound Healing and Collagen Formation

- ✓ Activation of **prolidase** enzyme which splits dipeptides that contain proline or hydroxyproline and provides proline for collagen formation
- ✓ **Glycosaminoglycan** synthesis is manganese dependent
  - ➢ Chondroitin sulfate
  - ➢ Keratan sulfate
  - ➢ Hyaluronic acid
- ✓ Rare **genetic abnormality of manganese** metabolism can result in prolidase deficiency and abnormalities of collagen synthesis



Nutrient Interactions: Manganese and Iron

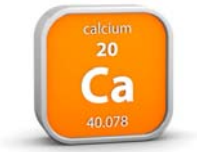
- ✓ Iron and manganese can share common absorption and transport pathways
- ✓ Absorption of manganese decreases as the iron increases
- ✓ Iron supplementation (60 mg/day for four months) was associated with decreased blood manganese levels and decreased MnSOD activity in white blood cells
- ✓ Intestinal absorption of manganese is increased during iron deficiency
- ✓ Increased ferritin associated with decreased manganese absorption
- ✓ Men absorb less manganese
- ✓ iron deficiency has been shown to increase the risk of manganese accumulation in the brain

Nutrient Interactions: Manganese and Magnesium

- ✓Supplemental magnesium (200 mg/day) has been shown to slightly decrease manganese bioavailability in healthy adults
  - ➢Decreases absorption or
  - ➢Increases excretion

Nutrient Interactions – Manganese and Calcium

- ✓ Supplemental calcium (500 mg/day) slightly decreased manganese bioavailability
- ✓ As a source of calcium, milk had the least effect, while calcium carbonate and calcium phosphate had the greatest effect
- ✓ Several other studies have found minimal effects of supplemental calcium on manganese metabolism



References for Manganese Nutrient Interactions

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Manganese Deficiency

Not common - more concern about toxicity

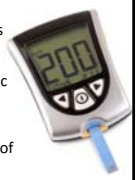
- ✓ Possible increased risk of osteoporosis, diabetes, epilepsy
- ✓ **Child on long-term TPN lacking manganese:** Bone demineralization and impaired growth that were corrected by manganese supplementation
- ✓ **Young men on a low-manganese diet:** Decreased serum cholesterol, a transient skin rash, and elevated blood levels of calcium, phosphorus, and alkaline phosphatase
- ✓ **Young women fed a manganese-poor diet:** Mildly abnormal glucose tolerance in response to an IV infusion of glucose
- ✓ http://www.drritamarie.com/go/LPIManganese

Osteoporosis

- ✓ **Women with osteoporosis:**
  - ➢ Found to have decreased plasma or serum levels of manganese
  - ➢ Enhanced plasma response to an oral dose of manganese
- ✓ **Postmenopausal women with and without osteoporosis:** No significant difference in plasma levels of manganese
- ✓ **A study in healthy postmenopausal women:**
  - ➢ A supplement containing manganese (5 mg/day), copper (2.5 mg/day), and zinc (15 mg/day) in combination with a calcium supplement (1,000 mg/day)
  - ➢ More effective than the calcium supplement alone in preventing spinal bone loss over a two-year period
  - ➢ The presence of other trace elements in the supplement makes it impossible to determine whether manganese supplementation was the beneficial agent for maintaining bone mineral density

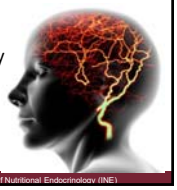
Diabetes Mellitus – Mixed Results

- ✓ In one study, whole blood manganese levels did not differ significantly between 57 diabetics and 28 non-diabetic controls
- ✓ Urinary manganese excretion tended to be slightly higher in 185 diabetics compared to 185 non-diabetic controls
- ✓ A case-control study of 250 diabetic and non-diabetic individuals found that type 2 diabetic individuals had higher serum manganese levels than non-diabetics
- ✓ A more recent study in 257 type 2 diabetics and 166 non-diabetic controls found lower blood levels of manganese in the diabetic patients
- ✓ A study of functional manganese status found the activity of the antioxidant enzyme, MnSOD, was lower in the white blood cells of diabetics than in non-diabetics
- ✓ Neither 15 mg nor 30 mg of oral manganese improved glucose tolerance in diabetics or non-diabetic controls when given at the same time as an oral glucose challenge
- ✓ Although manganese appears to play a role in glucose metabolism, there is little evidence that manganese supplementation improves glucose tolerance in diabetic or non-diabetic individuals



Epilepsy

- ✓ Manganese deficient rats are more susceptible to seizures than manganese sufficient rats
- ✓ Rats that are genetically prone to epilepsy have lower than normal brain and blood manganese levels
- ✓ Certain subgroups of humans with epilepsy reportedly have lower whole blood manganese levels than non-epileptic controls
- ✓ One study found blood manganese levels of individuals with epilepsy of unknown origin were lower than those of individuals whose epilepsy was induced by trauma (e.g., head injury) or disease
- ✓ A possible genetic relationship between epilepsy and abnormal manganese metabolism
- ✓ Manganese deficiency does not appear to be a cause of epilepsy in humans

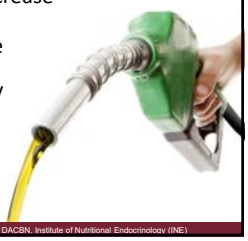


Toxicity – Inhaled Manganese

- ✓ Inhaled manganese is transported directly to the brain before it can be metabolized in the liver
- ✓ Neurologic problems are a well-recognized health hazard for people who inhale manganese dust, such as welders and smelters
- ✓ The symptoms of manganese toxicity generally appear slowly over a period of months to years
- ✓ Symptoms can resemble Parkinson's disease (manganism)
  - ➢ Tremors
  - ➢ Difficulty walking
  - ➢ Facial muscle spasms
  - ➢ Psychiatric symptoms: irritability, aggressiveness, and hallucinations
- ✓ Inflammation in the lungs is common, leading to cough, acute bronchitis, and decreased lung function

Methylcyclopentadienyl Manganese Tricarbonyl (MMT)

- ✓ Used in gasoline as an anti-knock additive in Canada for more than 20 years
- ✓ In 1995, MMT available in the US in unleaded gasoline
- ✓ Safety studies are not showing increase of manganese in the air
- ✓ The impact of long-term exposure to low levels of MMT combustion products has not been thoroughly evaluated and will require additional study



Ingested Manganese - 1

- ✓ A study of older adults in Greece found a high prevalence of neurological symptoms in those exposed to water manganese levels of 1.8-2.3 mg/liter
- ✓ A study in Germany found no evidence of increased neurological symptoms in people drinking water with manganese levels ranging from 0.3-2.2 mg/liter compared to those drinking water containing less than 0.05 mg/liter
  - ➢ None of the studies measured dietary manganese, so total manganese intake in these cases is unknown

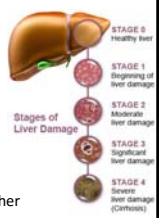
Ingested Manganese - 2

- ✓ More recent studies have shown that children exposed to high levels of manganese through drinking water experience cognitive and behavioral deficits
  - ➢ A cross-sectional study in 142 10-year old children, who were exposed to a mean manganese water concentration of 0.8 mg/liter, found that children exposed to higher manganese levels had significantly lower scores on three tests of intellectual function
  - ➢ Another study associated high levels of manganese in tap water with hyperactive behavioral disorders in children
  - ➢ These and other recent reports have raised concern over the neurobehavioral effects of manganese exposure in children
- ✓ A single case of manganese toxicity was reported in a person who took large amounts of mineral supplements for years
  - ➢ Another case was reported as a result of a person taking a Chinese herbal supplement
- ✓ Manganese toxicity resulting from foods alone has not been reported in humans, even though certain vegetarian diets could provide up to 20 mg/day of manganese

Intravenous Manganese

- ✓ Manganese neurotoxicity has been observed with excess in total parenteral nutrition
- ✓ Infants receiving manganese-containing TPN can be exposed to manganese concentrations about 100-fold higher than breast-fed infants
- ✓ Because of potential toxicities, some argue against including manganese in parenteral nutrition

Manganese Susceptibility Toxicity



- ✓ **Chronic liver disease:** Manganese is eliminated from the body mainly in bile. Thus, impaired liver function may lead to decreased manganese excretion. Manganese accumulation in individuals with cirrhosis or liver failure may contribute to neurological problems and Parkinson's disease-like symptoms
- ✓ **Newborns:** The newborn brain may be more susceptible to manganese toxicity due to a greater expression of receptors for the manganese transport protein (transferrin) in developing nerve cells and the immaturity of the liver's bile elimination system.
- ✓ **Children:** Compared to adults, infants and children have higher intestinal absorption of manganese, as well as lower biliary excretion of manganese. Thus, children are especially susceptible to any negative, neurotoxic effects of manganese. Indeed, several recent studies in school-aged children have reported deleterious cognitive and behavioral effects following excessive manganese exposure.
- ✓ **Iron-deficient populations:** Iron deficiency has been shown to increase the risk of manganese accumulation in the brain.

Adequate Intake (AI)

- ✓ No Recommended Dietary Allowance (RDA)
- ✓ Manganese requirements are increased in pregnancy and lactation

Age	Male	Female	Pregnant	Lactating
0-6 months	.003 mg	.003 mg		
7-12 months	0.6 mg	0.6 mg		
1-3 years	1.2 mg	1.2 mg		
4-8 years	1.5 mg	1.5 mg		
9-13 years	1.9 mg	1.6 mg		
14-18 years	2.2 mg	1.6 mg	2.0 mg	2.6 mg
19-50 years	2.3 mg	1.8 mg	2.0 mg	2.6 mg
51-70 years	2.3 mg	1.8 mg		
70+ years	2.3 mg	1.8 mg		

Food Sources

- ✓ Estimated US average dietary manganese intakes:
  - ➢ Range from 2.1-2.3 mg/day for men and 1.6-1.8 mg/day for women
  - ➢ People eating vegetarian diets and Western-type diets may have manganese intakes as high as 10.9 mg/day
- ✓ Phytic acid (found in beans, seeds, nuts, whole grains, and soy products) or foods high in oxalic acid (such as cabbage, spinach, and sweet potatoes) may slightly inhibit manganese absorption
- ✓ Tannins in tea may moderately reduce the absorption of manganese
- ✓ Iron, calcium, and phosphorus limit retention of manganese
- ✓ **Herbs:** Alfalfa, burdock root, catnip, chamomile, chickweed, dandelion, eyebright, fennel seed, fenugreek, ginseng, hops, horsetail, lemongrass, mullein, parsley, peppermint, raspberry, red clover, rose hips, wild yam, yarrow, and yellow dock
- ✓ **Foods:** Avocados, nuts and seeds, seaweed, whole grains, blueberries, legumes, dried peas, pineapples, and greens

Food	Serving Size	Cals	Amount (mg)
Cloves	2 tsp	11.5	2.53
Oats	0.25 cup	151.7	1.92
Brown Rice	1 cup	216.4	1.76
Garbanzo Beans	1 cup	269.0	1.69
Spinach	1 cup	41.4	1.68
Pineapple	1 cup	82.5	1.53
Collard Greens	1 cup	62.7	0.97
Cinnamon	2 tsp	12.8	0.91
Raspberries	1 cup	64.0	0.82
Black Pepper	2 tsp	14.6	0.74
Beet Greens	1 cup	38.9	0.74
Swiss Chard	1 cup	35.0	0.58
Strawberries	1 cup	46.1	0.56
Kale	1 cup	36.4	0.54
Turnip Greens	1 cup	28.8	0.49
Mustard Greens	1 cup	36.4	0.38
Summer Squash	1 cup	36.0	0.38
Turmeric	2 tsp	15.6	0.34
Sea Vegetables	1 TBS	10.8	0.31
Garlic	6 cloves	26.8	0.30
Basil	0.50 cup	4.9	0.24
Bok Choy	1 cup	20.4	0.24
Pumpkin Seeds	0.25 cup	180.3	1.47

http://www.drritamarie.com/go/WHFoodsManganese

Breast Milk and Formulas

- ✓ Infants are exposed to varying amounts of manganese depending on their source of nutrition
- ✓ Manganese concentrations in breast milk, cow-based formula, and soy-based formula range from 3-10 mcg/liter, 30-50 mcg/liter, and 200-300 mcg/liter, respectively
- ✓ Bioavailability of manganese from breast milk is higher than from infant formulas
  - ➢ Manganese deficiencies in breast-fed infants or toxicities in formula-fed infants have not been reported

Water

- ✓ Manganese concentrations in drinking water range from 1 to 100 micrograms (mcg)/liter; most contain less than 10 mcg/liter
- ✓ The US Environmental Protection Agency recommends 0.05 mg (50 mcg)/liter as the maximum allowable manganese concentration in drinking water

Manganese Supplements

- ✓ Forms
  - ➢ Manganese gluconate
  - ➢ Manganese sulfate
  - ➢ Manganese ascorbate
  - ➢ Amino acid chelates of manganese

Drug Interactions

- ✓ Magnesium-containing antacids
- ✓ Laxatives
- ✓ Tetracycline

May decrease the absorption of manganese if taken together with manganese-containing foods or supplements.

Bone/Joint Health Supplements

- ✓ Two studies have found that supplements containing a combination of glucosamine hydrochloride, chondroitin sulfate, and manganese ascorbate were beneficial in relieving pain due to mild or moderate osteoarthritis of the knee when compared to a placebo
- ✓ The dose of elemental manganese supplied by the supplements was 30 -40 mg/day for eight weeks
- ✓ No adverse effects were reported during either study, and blood manganese levels were not measured
- ✓ Neither study compared the treatment containing manganese ascorbate to a treatment containing glucosamine hydrochloride and chondroitin sulfate without manganese ascorbate
- ✓ It is impossible to determine whether the supplement would have resulted in the same benefit without high doses of manganese

Manganese Assessment

- ✓ Whole blood manganese levels are considered reliable
- ✓ Manganese in urine used to monitor exposure or excessive nutritional intake
- ✓ Hair manganese correlates well with manganese levels in other body tissues
  - ➢ Dark hair dyes can contain manganese and thus falsely elevate readings
  - ➢ In the case of extremely high manganese levels obtained from scalp hair, pubic hair should be tested as a control
  - ➢ Low hair manganese levels are considered reliable

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