The Adverse Effects of Manganese Deficiency on Reproduction and Health: A Literature Review

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Introduction

Manganese (Mn) is the 12th most abundant element in the earth's crust.[1] The total amount of manganese in the adult human organism has been determined to be about 10-20mg,[2-4] most of which is found in skeleton, liver, kidney, pancreas and the heart.[3] The rest is distributed widely throughout all the tissues and fluids, without notable concentration in any particular location, and with comparatively little variations among organs or with age.[2,5] However, manganese concentration tends to be higher in tissues rich in mitochondria than in the cytoplasm or in other organelles of the cell.[2,6,7] The number of manganese metalloenzymes is quite limited, whereas the enzymes that can be activated by manganese are numerous. They include hydrolases, kinases, decarboxylases and tranferases,[2,8] all of which are involved in multitude of metabolic processes, including bone formation, energy production, as well as both in protein and in fat metabolism.[2,9,10]

Manganese in Metabolic Processes

Bone Formation

The skeletal abnormalities of manganese deficiency have been found in all species studied. For example, in rats, mice, pigs, chicks, rabbits, sheep and guinea pigs, manganese deficiency, during gestation, have been associated with retarded and defective bone growth, enlarged hock joints, crooked and shortened legs and a variety of other leg deformities,[2,11-15] leading to severe neonatal locomotor ataxia.[2,16] Foetal manganese deficiency has also been associated with many other congenital abnormalities, such as defective development of the skull and the otoliths[2,17-20] characterized by a loss of equilibrium, ataxia, head retraction and tremors, increased susceptibility to stimuli and delayed development of the body-righting reflexes.[2,17,21-23] Furthermore, neonatal manganese deficiency has been linked with chondrodystrophy [2,24,25] perosis,[2,26] as well as with epiphyseal dysplasia.[2,19] In dogs, manganese deficiency has been found to result in abnormal bone, cartilage, and disc degeneration due to inadequate cartilage formation of the discs.[10,27] In view of the above findings, attention was turned to a possible involvement of manganese in the formation of organic matrix of the epiphyseal plate, an intergrating part of the growth zone, where the formation of the bone occurs in the cartilage at the epiphysis. If this process is inhibited in some manner, this will result in defective and retarded skeletal and bone maturation.[2,27] The final results show that the overall effects of manganese deficiency in a variety of skeletal abnormalities can now be explained in terms of its specific role in the synthesis of mucopolysaccharides, which are vital structural constituents of the cartilage.[2,28] The impairment in mucopolysaccharides synthesis associated with manganese deficiency has now been related to the activation of glycosyltransferases by this element, which are vital constituents both in polysaccharide and in glycoprotein formation.[2,27,28]

The critical sites of manganese function have been found to be related to the synthesis of chondroitin sulfate, the major polysaccharide of the cartilage, and the mucopolysaccharide most severely affected in manganese deficiency.[2,27-29] Chondroitin sulfate consists of a polypeptide backbone, to which is attached a carbohydrate side chain, composed of xylose and two molecules of galactose. To this is attached the main carbohydrate portion of

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the molecule, a repeating unit of glucuronate and N-acetyl-galactosamine. Research has now established, that manganese is the most efficient divalent cation in the activation of the glycosyltransferase enzymes, essential in the chondroitin sulfate formation .[2,27-29]

Manganese and Other Enzymatic Activities

In animal experiments, manganese deficiency have been found to result in abnormalities in cell function and ultrastucture, particularly involving the mitochondria. For example, when oxidative phosphorylation was studied in isolated liver in manganese deficient mice and rats, in both species, ratios of ATP formed to oxygen consumed were normal, but oxygen uptake was greatly reduced. Electron microscopy of these mitochondria revealed ultrastructure abnormalities, including elongation and reorientation of cristae.[2,30] Subsequently, it was confirmed by the same authors that dietary deficiency of manganese will lead to alterations in the integrity of all tissue cells examined, which included the liver, the kidney, the pancreas and the heart. In addition, the endoplasmic reticulum was found to be swollen and mitochondria was found to be irregular, with elongated stacked cristae in liver, heart, and kidney cells. Furthermore, there was found to be an overabundance of lipids in liver parenchymal and kidney tubule cells. The lowered oxidation in mitochondria from manganese deficient animals was believed by the authors to be related to all morphological changes observed.[2,31] Research has also established, that injected manganese is cleared rapidly from the bloodstream in three phases.[2,32] The first, and the fastest of these, is identical with the clearance rate of other small ions, suggesting the normal transcapillary movement. The second can be identified with the entrance of manganese into the mitochondria of the tissue, and the third has been found to indicate the rate of nuclear accumulation of the metal. These findings support the early preferential accumulation of manganese in the mitochondrial-rich organs of the body.[2,33] Manganese has also been found to play a part in the formation of thyroxine, the active principle of the secretion of the thyroid gland .[34]

Manganese and Superoxide Dismutase

As a mitochondrial element, manganese is also the key component of superoxide dismutase (SOD) found in mitochondria of the cells, which protects the fragile mitochondrial membrane from the attack of free radicals. Without manganese the mitochondrial SOD would simply be inactive and accumulation of free radicals would lead to severe membrane damage.[4,10,27,35] Other forms of superoxide dismutases, found in the cytosal, requires copper and zinc and iron for their activity.[10,27,35]

Manganese and Protein Metabolism

Manganese is important in the building and breakdown cycles of protein and nucleic acids, and for the RNA chain initiation.[10,27,36] The process of RNA synthesis consists of three major steps; initiation, elongation and termination. For the RNA chain reaction, manganese has been found to be a superior effector to any other metal, including magnesium. Research has also confirmed the findings establishing that manganese was found to be a far better effector in binding calf thymus RNA polymerase to DNA than magnesium.[27,37]

Manganese and Carbohydrate Metabolism

In a study on newborn guinea pigs, severely affected by manganese deficiency, they were found to exhibit aplasia, or marked hypoplasia of all cellular components of the pancreas. Compared to controls, the number of islet cells was found to be greatly reduced. The same effect was observed with beta cells, which was also found to be far less granulated than in control animals. In addition, young adult manganese-deficient guinea pigs were observed to have subnormal numbers of pan-

creatic islets, with less intensely granulated beta cells and more alpha cells than manganese-supplemented controls[2,27,38] When glucose was administered orally, or intravenously, the manganese-deficient animals revealed a decreased capacity to utilize glucose, and displayed a diabetic-like curve in response to the glucose loading. Manganese supplementation completely reversed the reduced glucose utilization in these animals.[27,38] Similar findings have been found in human subjects.[39,40] The role of manganese in glucose tolerance is not yet been well defined, but it is believed to be due to its vital role in the involvement with enzymatic reactions, particularly with glycosyltransferases, discussed previously.[2,27,28] Furthermore, it has been suggested that the impairment of glucose utilization in manganese deficiency may be related to some connective tissue defects that occur with defective carbohydrate metabolism, as decreased concentration of stainable mucopolysaccharides have been found on skins of young rats born to diabetic mothers.[27,41]

Manganese and Lipid Metabolism

An association between manganese and choline metabolism has been recognized already for some years.[2,27] For example, when rats were placed on a choline deficient diet, they exhibited lower hepatic manganese levels than those of controls. [2,27,42] Furthermore, it has been observed that choline deficiency produces similar changes in liver ultrastructure including perosis in chicks that have been found in manganese deficiency states.[2] As the result, it is suggested, that these two nutrients may be linked with some common pathway to ensure normal structure of the mitochondrial and cellular membranes, either directly through effects on the membrane synthesis, or indirectly through some alterations of the mitochondrial oxidations. [2,31]

Manganese and Prothrombin Formation

Since prothombin is a glycoprotein, its synthesis should also be influenced by manganese through its activating effects on glycosyltranferases. Evidence is now accumulating to that effect. Moderate manganese deficiency in chicks has been shown to reduce the clotting response of vitamin K, compared to that of chicks receiving ample dietary supply of manganese.[2,43] Moreover, a human patient suffering from both manganese and vitamin K deficiency was unable to elevate his depressed clotting protein given only vitamin K, until manganese was also restored to his diet.[43]

Manganese and Brain Function

Manganese has been found to stimulate adenylate cyclase activity in the brain and other tissues of the body.[27,44] This is of importance because cyclic-AMP plays a regulatory role in the action of several brain neurotransmitters by acting as a second messenger within cells in transmitting the messenger hormone.[27,34] One study with rats found that manganese was a potent stimulator of adenyte cyclase activity in different parts of the rat brain, whereas lead, mercury, zinc and copper were found to be powerful inhibitors of the enzyme. It was also established that the site of interaction of manganese with adenylate cyclase was found to be the catalytic subunit of the cyclase rather than the receptive or regulatory subunit.[27,45] Adenylate cyclase activities that specifically require manganese for their action have been found in animal studies both in striae cortex[34] and in neurospora cassa.[27,46] In humans, high manganese concentrations are usually found in basal ganglia, where the ion is believed to stimulate acetylcholine storage activity.[34] In humans, manganese deficiency has also been linked with reduced levels of the neurotransmitter, dopamine.[10]

Manganese and Schizophrenia

Manganese chloride was first tested and found effective in treating schizophrenia as the early as 1920s.[47,48] Somewhat later three micronutrients, in particular copper, zinc and manganese, started to

generate much research in a variety of mental disorders, particularly in schizophrenia.[27] Heilmeyer et al. presented one of the earliest studies implicating an excess of copper in 32 of 37 schizophrenics.[49] This was followed by Dr Pfeiffer and his colleagues who observed an excess of body copper and low manganese status in a variety of mental and physical disorders, including schizophrenias, depression, alcoholism, epilepsy, and in some infectious diseases and cancers.[27] In order to eliminate the excess body burden of copper, both manganese and zinc supplementation were used, as the two nutrients together were found to be far more effective for the copper elimination than either of them alone.[27,34,50-53] An additional study found considerably lower hair manganese levels in schizophrenic patients compared to controls.[54]

Other Manganese Responsive Syndromes

Epilepsy

Hurley and his colleagues were the first to demonstrate a significantly reduced seizure threshold in manganese deficient animals given manganese supplementation.[55] Further studies found considerably lower blood manganese levels in epileptic patients when compared to controls.[56-57] Thereafter several uncontrolled trials have found manganese supplementation helpful in controlling seizures, of both minor and major types, possibly due to its central role, with choline, in the control of membrane stability.[53]

Tardive Dyskinesia

The side effects of prolonged medication with neuroleptic drugs are known to lead to tardive dyskinesia. This condition is sometimes reversible after cessation of medication. However, in many subjects, this condition seems to become irreversible. Research has now shown that neuroleptics are able to chelate body manganese,[58] binding it electrochemically, thus making it unavailable as an enzyme activator.[59] Research by Kunin[60] found when treating 15 patients suffering from tardive dyskinesia with manganese supplementation, that seven were cured outright, three were much improved, four were improved, and only one was unimproved. As the result, it has been suggested that manganese can be of value in the treatment of tardive dyskinesia, as well as preventing this iatrogenic disorder from occurring.[27] In addition to conditions mentioned above, manganese deficiency has been associated with back ache, due to its essential role in the cartilage formation.[27,61] Also, manganese deficiency has been associated with cancer formation, due to its central role in superoxide dismutase, which protects the cell nucleus and the mitochondria from free radical formation.[10] Manganese deficiency has also been linked with heart disease, as manganese has been found to be an equally effective calcium antagonist as modern drugs.[10] In addition, a study reported hair manganese levels of both male and female patients diagnosed with multiple sclerosis (MS) to be half of that found in control subjects.[62]

Manganese and Reproductive Function

The earliest studies on animals were able to demonstrate that a manganese deficient diet can lead to defective ovulation, testicular degeneration, and to offspring mortality.[63-66] In the female, three stages of manganese deficiency are now recognized. In the least severe stage the animals may give birth to young with a variety of malformations. In the second, more severe stage, the young are born dead, or die shortly after birth. In the third, or in the acute stage of manganese deficiency, estrous cycles are absent or irregular, the animals will not mate, and sterility results. A delayed opening of the vaginal orifice may also occur.[67] The severely manganese deficient male animals exhibit sterility and absence of libido, associated with seminal tubular degeneration, lack of spermazoa, and accumulation of degenerating cells in the epididymis.[67,68] The precise locus mode

of action of manganese in preventing the reproductive defects in both male and female animals has not yet been established. However, a suggestion has been put forward that the lack of manganese may inhibit the synthesis of cholesterol and its precursors, thus limiting the synthesis of sex hormones and possibly other steroids with the consequent infertility.[69]

The Teratogenic Effects of Manganese Deficiency

As discussed previously, it is now known, using animal experiments, that maternal manganese deficiency during embryonic development produces a variety of irreversible congenital malformations in the offspring including multiple skeletal and joint malformations, as well as a variety of structural defects of the skull and the otoliths, resulting in ataxia, loss of equilibrium and tremors.[2,10-29] Similar findings have now been established in the human offspring.

Saner and co-workers[70] investigated hair manganese status of mothers and their infants at delivery using flameless atomic absorption technique. The study was carried out on 31 full-term, 18 pre-term, and 12 newborn infants with congenital malformations and their mothers. The types of congenital malformations in this study included anencephaly, meningomyelocele, double cleft lip and cleft palate, spina bifida occulta, hydrocephalus, hermaphroditism, and digital aplasia of both hands and feet. The control group consisted of 11 nulliparous women of comparable ages. None of the mothers showed any clinical evidence of nutritional deficiencies. The final results found significantly lower hair manganese concentrations both in the mothers and in the infants with congenital malformations when compared to the control subjects. In addition, it was found that hair manganese levels in both full-term and pre-term infants with congenital malformations were almost identical, suggesting that manganese transfer seems to occur to the foetus at an early stage, well before the third trimester of the pregnancy.

The study concludes that early gestational manganese deficiency can indeed be a potential factor in intrauterine malformations. Additionally, the interrelationship between manganese transfer from the mother to the foetus seems to be regulated by a homeostatic mechanism which is directly dependent on the manganese status of the mother. Furthermore, that low prenatal maternal hair manganese status may provide a reliable indicator of potential malformations in the offspring.[70]

Additional research has also shown that, through certain enzymes, manganese seems to affect the glandular secretions underlying maternal instinct.[34,71,72] This has been observed repeatedly in animal studies which have found that manganese deficient mothers do not nurse their pups readily.[72] The stress on the female manganese stores appears to be the greatest during the gestational period when the fetal brain and other organs are developing.[73] If during this most critical time of cellular development an essential element, such as manganese is deficient, this can lead not only to a variety of physical malformations, but also to deficiencies in mental functioning. The brain, after all, requires the same nutrients for cellular development as other fetal organs. In animal studies, maternal maganese deficiency has been found invariably to lead to a variety of behavioural disorders in the offspring, mainly related to the incomplete development of the otoliths.[72,73] However, other studies have linked maternal manganese deficiency to other subtle central nervous system development disorders, including inadequate clasping and righting performance.[72] In conclusion, even though the often bizarre behavioural patterns found in manganese deficient offspring can be mostly related to the inner ear changes, there still remains enough circumstancial evidence between maternal manganese deficiency and fetal

brain development, indicating that maternal manganese deficiency may also lead to other subtle behavioural and central nervous system dysfunctions in the offspring.[73]

Manganese and Nutrition

Absorption

Manganese is absorbed slowly and poorly throughout the length of the small intestine by a two-step mechanism involving initial uptake from the lumen, then transfer across the mucosal cells into the liver and other organs.[2,10,74] Manganese absorption is dependent largely on the concentration of manganese already found in the body, i.e. the amount of manganese absorbed will not increase appreciably with dietary increases above that needed for normal body functioning.[2]

Within the intestinal mucosa, manganese has been found to compete with iron for common binding sites for absorption, manganese having far less affinity to the carrier proteins than iron.[10,27,74,75] Manganese absorption is also negatively related to the presence of other trace minerals, such as copper, zinc, cobalt, phosphorus and calcium, as well as soyprotein,[10,27] whereas lecithin, choline and ethanol seems to enhance intestinal and liver uptake of manganese.[10] Most of the manganese ions which are absorbed into the portal circulation are almost completely removed by the liver and excreted into the bile. If bile flow is for some reason blocked and the hepatic pathway is overloaded, excretion takes place via the pancreatic juice, the duodenum, the jejenum and, to a smaller extent, via the terminal ileum.[10,27] This highly efficient manganese excretory mechanism ensures that manganese toxicity through the use of oral supplementation is highly improbable.[10,27] In fact, manganese toxicity arising from excessive oral intake has never been recorded.[2] However, chronic manganese poisoning has been reported to occur from industrial sources, particularly among miners following prolonged working with manganese ores, where the excess manganese oxide dust has entered into the body via lungs from the highly contaminated working environment. Chronic manganese poisoning is characterized by a severe psychiatric disorder (locura manganica) resembling schizophrenia, followed by a permanently crippling neurological disorder, clinically similar to Parkinson's disease.[2,34]

Manganese Sources and Needs

The minimum dietary requirement of manganese varies within species and the genetic strain of the animal.[2] Even though manganese is considered an essential trace element, no official daily recommendation of manganese for humans has been set.[4] However, about 4-5 mg of manganese daily is generally accepted to be an average daily requirement, as a healthy human body uses approximately 4 mg manganese each day in bone/cartilage replacement, lipid and carbohydrate metabolism, as well as in other manganese-dependent enzymatic processes.[34,76,77]

An average Western diet has been calculated to provide between 1-8 mg of manganese daily. Among tea-drinking nations the amount has been thought to be about 4.6 mg, as tea leaves are known to contain a fair amount of the mineral.[77] Other rich food sources are nuts, whole grains, spices and legumes, while meat, fish and dairy products contain only insignificant amounts.[27,53,78] Only about 3-5% of dietary manganese is absorbed, so daily intakes must be sufficient to allow for the losses.[4,77]

Is Manganese Deficiency Possible?

It is generally believed that manganese deficiency cannot arise in humans because the element is widely distributed in foodstuffs. However, it has now been found that most Western diets, even best planned, tend to be deficient in this important trace mineral, as many of our most frequently eaten foods, such as meat, fish and dairy products contain only insignificant traces of manganese.

As far as natural sources of manga-

nese are concerned, foods that are considered to be high in manganese, such as whole grains, legumes and nuts, they will contain only the amount of manganese that is available in the soil they have been grown in. Unfortunately, current farming methods, particularly the excessive use of agrochemicals, are known to cause severe manganese deficiencies, both in the soil and in the crop it yields. In fact, a recent global investigation on micronutrient status of soils and plants have found a particularly low level of manganese, as well as zinc and iron in the samples studied.[79,80] Furthermore, liming the soil greatly increases the foliage, with the corresponding depletion of manganese.[27,34] Insecticides, which are used widely in the modern agriculture, are known to inactivate choline containing enzymes, which in turn prevents the uptake of manganese by the plants.[71] The present trend of an increased consumption of excessive sugar, as well as processed and refined foods, further reduces the manganese status. For example, the germ of the grain, which can be high in manganese, is discarded during the milling process.[4,27,34] Therefore, the combination of the use of agrochemicals with food processing can hardly provide adequate dietary intake of manganese, particularly when one considers that only 3-5% of the mineral is absorbed.

Discussion

The main manifestations of foetal manganese deficiencies, namely gross skeletal and cartilage abnormalities, defective development of the skull and the otoliths, ataxia, defects of lipid and carbohydrate metabolism, and depressed or disturbed reproduction function, have been found in all animal species studied. In addition, manganese deficiency has been associated with impaired mitochondrial oxidation and glucose tolerance, inadequate protein and nuleic acid synthesis, hydrocephalus, spina bifida, hermaphroditism, digital aplasia of both hands and feet, defective blood clotting, back problems, convulsions, as well as with other neurological disturbances.

Regardless of the seriousness of manganese deficiency, it is most suprising to find that there are still no official recommendations for this important trace mineral. Particularly when taking into account the most serious and irreversible manifestations of foetal manganese deficiencies found in animal studies, the general lack of concern for a possible human manganese deficiency during the gestational period is difficult to comprehend. After all, even though human foetuses are slightly higher up in the phyletic tree than animal foetuses, that can not make them invulnerable to gestational manganese deficiencies. Already studies on humans have shown that mothers with infants with congenital malformations have been found to have far lower hair manganese concentration than controls, indicating that maternal manganese deficiency can be a cause for malformed human offspring.[70] Furthermore, gestational manganese deficiency can also lead to the development of other disorders, such as changes in the inner ear function, ataxia and diabetes. As mentioned before, contrary to current belief, nutritional manganese deficiency in humans can easily arise due to its poor absorption rate, combined with modern food production which strips manganese from the foodstuffs from the soil to the table. Manganese absorption is also greatly hindered by the presence of other trace minerals, particularly of iron, as these two metals compete for the same binding sites, manganese having far inferior affinity to the carrier protein than iron. This observation is particularly noteworthy, as during pregnancy most women are routinely prescribed iron supplementation which further reduces the body manganese status. For the reasons above, one could suggest that gestational manganese deficiency could really be more a norm than a rarity, particularly as animal studies have shown

that the stress on the female manganese stores are the greatest during the gestational period.[72]

Summary

Even though manganese has been known for a long time to be officially an essential trace element, it is still greatly underrated. One of the reasons may be the assumption that as the trace mineral is fairly widely distributed in most foodstuffs so manganese deficiencies will not arise, therefore there is nothing to worry about. Unfortunately this assumption is not correct. Even if dietary manganese deficiency was not detrimental to healthy non-pregnant adults, an adequate amount of this trace mineral would be absolutely vital during gestation for normal foetal growth and development. This being the case, all would-be mothers should be informed about the importance of adequate dietary manganese before and during pregnancy.

The medical profession is already stressing the importance of folic acid in the prevention of spina bifida. Similar action should be taken with manganese. In order to assess body manganese status, blood tests are unfortunately misleading, as normal human blood shows widely varying concentrations of the trace element, with higher concentrations in the red cells than in the serum.[2,82-86] However, hair mineral analysis, when using correct measures and sample preparations, is an extremely valuable diagnostic tool for obtaining body manganese status.[70,87-89]

Hair mineral analysis is also an outstanding way to find out whether the would-be mother may also be suffering from heavy metal contamination, such as lead and/or cadmium, both known to lead to low birth-weight infants.[89-90] Low birth-weight in turn has been associated, in later years, with a great variety of both neurological and physical defects.[89-96] If hair mineral analysis records low manganese status, manganese supplementation should be prescribed. Fortunately manganese is well tolerated, due to its highly efficient excretory mechanism, its absorption not increasing above that which the body needs. However, it should be noted, that most trace metals exert an inhibitory effect on the absorption of others. Therefore, it would be prudent to prescribe a balanced vitamin/mineral combination, which includes sufficient manganese, in order to avoid creating deficiencies in others. Particularly, an adequate dietary zinc status is known to be absolutely vital both for reproduction and for healthy foetal development.[90,96] In conclusion, manganese, with other trace elements and vitamins, is absolutely essential in the development of a healthy baby. Therefore, all would-be mothers must be made immediately aware of this most important fact, as they have now been made aware of the importance of folic acid in the prevention of spina bifida. As seen from this discussion, the lack of manganese can also lead to a variety of foetal malformations. The sooner this point is put forward, the better, as the latest U.K. statistics reveal that out of every 100 live births, six babies are now born either with 'minor' or 'major' physical malformations. Furthermore, one in four babies are now born with some degree of learning disability and/or mental deficiency.[97] These statistics are absolutely appalling! After all, our children are our future, so we must to try our utmost to secure their future. Presently, because of our ignorance of basic reproductive biochemistry, we seem to be re-populating our world with the physically sick and the mentally infirm.

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