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Manganese in health and diseases: A review

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Abstract
Manganese (Mn) is an important trace metal for human health and it plays a significant role in metabolism and in antioxidant systems, diabetes mellitus (DM) and cardiac functions. Pre DM is said to develop when manganese level are at the lowest normal range. Regulation of Mn level at the optimum may prevent pre diabetes and diabetes. Oral Mn supplementation has emerged as the recent preventive measure for DM in whom deficiency of Mn exist. Many studies have been done in the laboratory animals on the beneficial effect of Mn supplementation mostly in the diabetic induced rats but there are lacunae on such studies in humans. While Mn deficiency affects carbohydrate metabolism, its excess affects many organs such as kidney, liver and central nervous system (CNS). Mn metabolic disturbances also leads to Parkinson's Disease (PD. known as Manganism). This review article summaries the research findings during the last two decades on the role of Mn in the metabolic disturbances notably in carbohydrate metabolic regulation as well as in other organ specific functions. The contents of this review article will help future researchers to undertake more work on the role of Mn in human health. Large scale studies involving humans on supplementation studies will enable to fix an optimum level of Mn consumption for treating patients found to have low Mn level.

Keywords: manganes, DM, MnSOD, CRF, PD, manganism, CNS

Introduction
Human body contains almost all metals found in nature. Metals help the body in the healthy functioning of brain and other organs. They play a significant role in the formation of blood, bones, teeth, tissues, osmoregulation of body fluids and the control of all physiological functions; however they are required only in trace amounts. The sources for all the metals are typhically followed in diverse diets. Both deficiency and excess by supplementation causes health problems.

Among the macro metals, Calcium (Ca), Phosphorous, Sodium and Potassium and non metals Chlorine and Sulphur play significant role in health and human diseases. A micro element is defined when its level in circulating blood plasma is <100 ppm. The important micro minerals are Iron (Fe), Copper (Cu), Mn, Iodine, Zinc (Zn), Selenium, Cobalt, Molybdenum and Chromium and all of them play a greatly significant role in human health and diseases.

Manganese in general health
Several epidemiological studies have indicated that a number of trace elements may play a role in type 2 diabetes mellitus (T2DM). No statistical evidence for associations between blood levels of Arsenic, Bromine, Cadmium, Cesium, Chromium, Cu, Gallium, Gold, Mn, Mercury, Molybdenum, Nickel, Rubidium, Selenium, Strontium, Tantalum, Thallium, Tin and Zn and T2DM prevalence. After corrections for multiple testings, associations remained significant for Ca and Lead and borderline significant for Mg, Silver and Boron and with increasing disease duration, higher Ca levels were observed [1].

Mn is an important metal for human health, being absolutely necessary for development, metabolism and the antioxidant system. Nevertheless, excessive exposure or intake may lead to a condition known as manganism, a neurodegenerative disorder that causes dopaminergic neuronal death and parkinsonian-like symptoms [2].

Exposure to Mn causes clinical signs and symptoms resembling, but not identical to, PD. Recent data suggest that Mn accumulates substantially in bone, with a half-life of about 8-9 years expected in human bones. Mn toxicity has been associated with dopaminergic dysfunction by recent neurochemical analyses and synchrotron X-ray fluorescent imaging studies. Evidence from humans indicate that individual factors such as age, gender, ethnicity, genetics, and pre-existing medical conditions can have profound impacts on Mn toxicities. In addition to body fluid-based biomarkers, new approaches in searching biomarkers of Mn

exposure include its levels in toenails, non-invasive measurement of Mn in bone, and functional alteration assessments. Comments and recommendations are also provided with regard to the diagnosis of Mn intoxication and clinical intervention. Finally, several hot and promising research areas in the next decade are emerging [3].

Manganese superoxide dismutase (MnSOD) is the mitochondrial enzyme that disposes of superoxide generated by respiratory chain activity. Of all electrons passing down the mitochondrial respiratory chain, 1-2% are diverted to form superoxide; thus production of hydrogen peroxide occurs at a constant rate due to MnSOD activity. Patients with complex I (NADH-CoQ oxidoreductase) deficiency show variable hyperinduction of MnSOD that is at least partially dependent on the extent of disturbance of redox state. This in turn appears to result in production of excess hydroxyl radicals, which are damaging to proteins, lipids and DNA. An alternative method of protection from oxygen radicals is employed by complex I-deficient cell types that do not induce MnSOD in that they show induction of the B cell lymphoma protein 2 (Bcl-2) [4].

Digestive disturbances in the calves were accompanied by changes in levels and magnitude of Na+/K+ ratio, Mg, Fe, Cu, Mn and Zn contents in blood, liver and kidneys as well as Ca++/Pi ratio in mitochondria and cytosol of liver and jejunum mucose layer cells in comparison with clinically healthy animals [5].

Manganese and Diabetes Mellitus

Blood and tissue levels of Mn are lower in T2DM and atherosclerosis patients compared with healthy subjects. Adiponectin has anti-diabetic and anti-atherogenic properties. Impairment in Disulpide –bond like praotein (DsbA-L) is associated with low adiponectin levels and diabetes. Mn supplementation resulted in higher adiponectin and lower Intracellular Adhesion Molecule-1 (ICAM-1) and lower creatinine blood levels compared to those in control Zucker Diabetic Fatty (ZDF) rats. Mn-supplemented rats also caused reduced oxidative stress (OS) and NADPH oxidase, and higher DsbA-L expression in the liver of ZDF rats compared to those in livers of control rats; however, Fe levels in liver were lower but not significant. Similarly, treatment with high glucose caused a decrease in DsbA-L, which was prevented by Mn supplementation in Human ambilical vein endothelial cells (HUVEC) and adipocytes. Mechanistic studies with DsbA-L siRNA showed that the beneficial effects of Mn supplementation on Reactive Oxygen Species (ROS), NADPH Oxidase 4 protein (NOX4), and ICAM-1 expression were abolished in DsbA-L knock-down HUVEC [6].

Older adults can experience glucose metabolism dysfunction, and although Mn may help regulate glucose metabolism, there is little information regarding this association among older people. Based on the World Health Organisation (WHO) criteria, prediabetes was observed in 15.1% of men and 13.4% of women, while diabetes was observed in 30.0% of men and 34.4% of women. The lowest prevalence of diabetes among men occurred at a moderate range of serum Mn. Therefore, appropriate serum Mn levels may help prevent and control prediabetes and diabetes [7].

The Mn treated group fed high fat had improved glucose tolerance (24% decrease in fasting glucose and 41% decrease in the area under the glucose curve), comparable with mice on normal chow and increased serum insulin levels. Isolated islets from the Mn-treated group exhibited improved insulin secretion, decreased lipid peroxidation and improved mitochondrial function. Hence, MnSOD metallation and activity can be augmented with Mn supplementation in normal mice on normal chow and Mn treatment can increase insulin secretion to improve glucose tolerance under conditions of dietary stress [8].

OS is an important component of diabetes and its complications. Mn is the key component of the MnSOD which, plays a key role in the superoxide uncoupling protein 2 (UCP-2) pathway in inhibiting glucose-stimulated insulin secretion (GSIS). The interactions of Mn with ascorbate and other components of this pathway have not been defined in T2DM. Absence of significant OS in the mitochondria, probably excluding a role for UCP-2-superoxide pathway in the inhibition of GSIS, calling for caution in the precocious conclusion that interruption of UCP-2 activity may provide a viable strategy to improve beta-cell dysfunction in T2DM [9].

The amounts of immunoreactive arginase protein in livers of control and diabetic rats were similar. The specific activity of purified preparations of arginase from diabetic rats was approximately 1.5-fold higher than that from control rats. Mn, a cofactor for arginase, was elevated on the 4th day post-streptozotocin injection and remained elevated (maximally 1.6-fold) for at least 13 days. Most of the Mn in control and diabetic liver cytosols were associated with macromolecules and eluted with arginase activity upon gel filtration [10].

Mutations in the SLC39A14 gene have been linked to Mn accumulation in the brain and childhood-onset parkinsonism dystonia. It has therefore been suggested that SLC39A14 deficiency impairs hepatic Mn uptake and biliary excretion, resulting in the accumulation of Mn in the circulation and brain. Mice develop markedly increased Mn concentrations in the brain and several extra hepatic tissues, as well as motor deficits that can be rescued by treatment with the metal chelatorNa2CaEDTA [11].

Mn becomes toxic at elevated levels. Loss-of-function mutations in SLC30A10, a cell-surface-localized Mn efflux transporter, cause a heritable Mn metabolism disorder resulting in elevated Mnlevels and parkinsonian-like movement deficits. The underlying disease mechanisms are unclear and therefore, treatment is challenging. Importantly, a low-Mn diet produced lower tissue levels in the knock-outs and rescued the phenotype, suggesting that Mn toxicity was the underlying cause. This discovery highlights the importance of determining the role of thyroid dysfunction in the onset and progression of Mn induced disease and identifies Slc30a10 knock-out mice as a new model for studying thyroid biology [12].

Conjugation of Mn to Nano diamonds resulted in improved longitudinal and transverse relaxivity efficacy over unmodified MnCl2 as well as clinical contrast agents. Following intravenous administration, nano diamond-Mn complexes outperformed current clinical contrast agents in an orthotropic liver cancer mouse model while also reducing blood serum concentration of toxic free Mn ions. Thus, nanodiamond-Mn complexes may serve as more effective dual mode MRI contrast agent, particularly in cancer [13].

Manganese, central nervous systems and hepatic encephalopathy

Oral supplementation of Mn with galactose and uredines led to improvement of the transferrin isoform pattern within 14 days of treatment initiation and oral Mn has only recently been added to the treatment. These results suggest SLC39A8

deficiency can cause both a type II Congenital disorder of glycosylation (CDG) and Leigh-like syndrome, possibly via reduced activity of the Mn dependent enzymes β-galactosyltransferase and mitochondrial MnSoD [14].

Mn overexposure induced neurological damages, which could be potentially protected by sodium para-aminosalicylic acid (PAS-Na). Mn overexposure significantly increased Mn in most organs, Fe and Zn in liver, Fe and Mg in blood; however decreased Fe, Cu, Zn, Mg and Ca in cortex, Cu and Zn in kidney, Cu and Mg in iliac bone, and Zn in blood. Excessive Mn exposure disturbed the balance of other metal elements but PAS-Na post-treatments could restore these alterations [15].

Hepatic encephalopathy is a common complication in cases of liver damage; it results from several factors, including the accumulation of toxic substances in the brain, e.g.Mn, ammonia and glutamine. Bumetanide produced no effect on glutamine accumulation; however, because of bumetanide treatment, Mn was increased in the brain, and also the activity of Gamma-Glutamyl Transferase (GGT) in plasma, leading to the influence of bumetanide and similar diuretics on liver function and Mn homeostasis should be further studied [16].

Malondialdehyde (MDA) significantly increased in both heart and liver of the animals after combined exposure to metals. Heart MDA correlated with blood Cd, Pb, and Mn and liver MDA with blood Cd. Aspartate Aminotransferase (AST) activity and bilirubin concentration also increased significantly in the animal group exposed to all three metals and correlated positively with blood Cd, Pb, and Mn. A study has confirmed the synergistic effect of Cd, Mn, and Pb combination on the increase in heart MDA. A similar synergy was observed for Pb+Mn in the increase of serum Alanine Aminotransferase (ALT) activity as an indicator of liver function [17].

Mn is a component in many enzymes, which play an important role in counteracting OS. *In vitro* experiments have revealed the ability of Mn to scavenge oxygen free radicals generated in differently mediated lipid peroxidation (LPO) conditions. Mn has the protective effect in Cd-induced systemic toxicity in mice. Further investigations are required on the relation between Mn accumulation and resistance to OS and on the factors influencing Mn/Cd transport in rodents to elucidate the molecular basis of this protective effect [18].

Dietary Mn supplementation decreased Fe concentration in duodenum and liver of hens, which may be related to the alteration of divalent metal transporter-1(DMT1) and Ferroportin-1(FPN1) expression in these tissues [19].

Ochratoxin A (OTA) is a natural mycotoxin, involved in the development of important human and animal diseases. Animals treated with OTA presented hypertension and reduction of glomerular filtration rate (GFR). These effects are most probably related to an increase in the reactive oxygen species (ROS) productions. In fact treatment with rMnSOD restored the levels of blood pressure and GFR simultaneously. Moreover OTA induced alteration on glomerular and tubular degeneration and interstitial infiltrates and that use of rMnSOD combined with OTA prevent this renal histological damage confirming the potential therapeutic role in the treatment of rMnSOD OTA nephrotoxicity [20].

Mn excess may be neurotoxic to humans, affecting specific areas of the CNS. However, relatively little is known about its physiological and/or toxicological effects, and very few data are available concerning the role of Mn in chronic renal failure (CRF). The CRF patients had higher plasma levels of creatinine, urea, uric acid and Mn and a lower GFR than the controls. Plasma Mn was positively correlated with creatinine, plasma urea and plasma uric acid and was negatively correlated with the GFR and the intake of energy and macronutrients. CRF in predialysis patients is associated with increases in circulating levels of Mn [21].

Prolonged exposure to environmental toxicants, such as Mn,Hg, or Pb, however, can lead to dysregulation of these neurochemicals and subsequent neurotoxicity. While the ability of these metals to disrupt the regulation of Glu, Gly and Gamma Amina Butyric Acid (GABA) have been studied, few articles have examined the collective role of these amino acids in the respective metal's mechanism of toxicity. For each of the neurotransmitters above, a brief synopsis of their regulatory function, including the importance of transport and re-uptake in maintaining their optimal functions are required [22].

MnSOD is essential for life as dramatically illustrated by the neonatal lethality of mice that are deficient in MnSOD. In addition, mice expressing only 50% of the normal compliment of MnSOD demonstrate increased susceptibility to OS and severe mitochondrial dysfunction resulting from elevation of ROS. Tyrosine nitration and inactivation of MnSOD would lead to increased levels of superoxide and concomitant increases in Peroxynitrite oxidation (ONOO) - within the mitochondria which, could lead to tyrosine nitration/oxidation of key mitochondrial proteins and ultimately mitochondrial dysfunction and cell death [23].

Mn neurotoxicity displays non-motor dysfunction and motor impairment like PD, and is called as Manganism. Circadian disruption is a non-motor symptom found in PD and Manganism. Clock genes are essential to drive and maintain circadian rhythm, but little is known about Mn exposure on circadian clock genes expression. Both the brain and liver are targets of Mn and repeated Mn administration could affect clock gene expression in the hypothalamus, brain and liver [24].

Hepatic encephalopathy is a serious complication of liver failure. Until now, the precise pathophysiologic mechanisms are not fully determined. It has been demonstrated that Mn plays an important role in the pathogenesis of hepatic encephalopathy. The mean serum Mn level was significantly higher in cirrhotic patients than in controls and in cirrhotic patients with encephalopathy than in those without encephalopathy. It was also significantly higher in patients with advanced grading of hepatic encephalopathy. Serum Mn level was positively correlated to number of recurrences of encephalopathy during a 6-month follow-up period. Serum Mn levels were able to predict recurrence of hepatic encephalopathy within 6 months following the episode. Serum Mn levels are positively correlated to the modified Child-Pugh score of cirrhosis as well as grading and number of recurrences of hepatic encephalopathy. Higher Mn levels seem to be related to worsening of the condition, and its measurement may be used as a predictor of repeated recurrences [25].

Mn levels are tightly regulated, as high levels of Mn result in accumulation in the brain and cause a neurological disease known as manganism. Manganism shares many similarities with PD, both at the physiological level and the cellular level. Exposure to high Mn-containing environments increases the risk of developing manganism. Mn is absorbed primarily through the intestine and then released in the blood. Excessive Mn is secreted in the bile and excreted in feces. Mn enters and exits cells through a number of non-specific importers localized on the cell membrane. Mutations in one of the Mn exporters, SLC30A10 (solute carrier family 30, member 10),

result in Mn induced toxicity with liver impairments and neurological dysfunction. Four PD genes have been identified in connection to regulation of Mn toxicity, shedding new light on potential links between manganism and PD [26].

Impaired cellular homeostasis of metals, particularly of Cu, Fe and Mn may trigger neurodegeneration through various mechanisms, notably induction of OS, promotion of α-synuclein aggregation and fibril formation, activation of microglial cells leading to inflammation and impaired production of metalloproteins [27]. Hereditary hemochromatosis, an iron overload disease associated with excessive intestinal iron absorption, is commonly caused by loss of Hemochromatosis (HFE) gene function. Both iron and manganese absorption are regulated by iron status, but the relationships between the transport pathways of these metals and how they are affected by HFE-associated hemochromatosis remain poorly understood. Although the influence of HFE deficiency on dietary iron absorption has been characterized, potential effects on Mnmetabolism have yet to be explored [28].

Mn is an industrial neurotoxicant in humans and animal models limited to rodent species. Thiopental increased the duration of loss of righting reflex in Mn-treated chicks when compared with that of the control group. Chlorpromazine challenge of Mn-treated chicks significantly increased the depressant action of Mn in the open-field arena and increased the duration of tonic immobility response produced by the metal [29].

Hepatic encephalopathy is a major complication of cirrhosis. Ammonia and Mn have been associated with hepatic encephalopathy underlying mechanisms. Motor impairment and brain edema are common signs of hepatic encephalopathy. Mn favoured ammonia and glutamine accumulation in brain, and possibly their subsequent deleterious effects, as evidenced by the fact that Mn and ammonia accumulation in the brain of cirrhotic rats severely affected motor function, suggesting that even when controlling ammonia levels in cirrhotic patients, reduction of Mn intake is also a potential strategy to be considered in clinical practice [30].

Mn is a key constituent of clue enzymes in the central nervous system, contributing to antioxidant defenses, energetic metabolism, ammonia detoxification, among other important functions. Until now, Mn transport mechanisms are partially understood; however, it is known that it shares some mechanisms of transport with Fe. CNS is susceptible to Mn toxicity because it possesses mechanisms that allow Mn entry and favor its accumulation. Cases of occupational Mn exposure have been extensively reported in the literature; however, there are other ways of exposure, such as long-term parental nutrition and liver failure. Manganism and hepatic encephalopathy are the most common pathologies associated with the effects of Mn exposure. Both pathologies are associated with motor and psychiatric disturbances, related in turn to mechanisms of damage such as OS and neurotransmitters alterations, the dopaminergic system being one of the most affected. Although manganism and PD share some characteristics, they differ in many aspects. It is necessary to find an effective therapeutic strategy to decrease Mn levels in exposed individuals and to treat Mn long term effects. In the case of patients with chronic liver failure it would be worthwhile to test a low-Mn diet in order to ameliorate symptoms of hepatic encephalopathy possibly related to Mn accumulation [31].

Mn in excess is neurotoxic and causes a CNS disorder that resembles PD. Mn highly accumulates in astrocytes, which renders these cells more vulnerable to its toxicity. Consistent with this vulnerability, Mn has been shown to cause histopathological changes in astrocytes (Alzheimer type II change), generates OS and bring about mitochondrial dysfunction, including the induction of the mitochondrial permeability transition (mPT) in astrocytes. In addition to manganism, increased brain levels of Mn have been found in hepatic encephalopathy, a chronic neurological condition associated with liver dysfunction.Mn exposure results in astrocyte swelling and such swelling, at least in part, may be caused by OS and/or mPT. Astrocyte swelling by Mn may represent an important aspect of Mn neurotoxicity, and may be a factor in low-grade brain edema associated with chronic hepatic encephalopathy [32].

Manganese and Liver

The role of trace elements in the pathogenesis of liver cirrhosis and its complications is still not clearly understood. Serum concentrations of Zn was significantly lower in patients with liver cirrhosis in comparison to controls. Serum concentrations of Cu was significantly higher in patients with liver cirrhosis as well as Mn. The concentration of Mg was not significantly different between patients with liver cirrhosis and controls. There were no differences in the concentrations of Zn, Cu, Mn and Mg between male and female patients with liver cirrhosis. The correction of trace elements concentrations might have a beneficial effect on complications and maybe progression of liver cirrhosis. It would be recommendable to provide analysis of trace elements as a routine [33].

Mn is a required element and a metabolic byproduct of the contrast agent mangafodipirtrisodium (MnDPDP). The Mn released from MnDPDP is initially sequestered by the liver for first-pass elimination, which allows an enhanced contrast for diagnostic imaging. The administration of intravenous Mn impacts its homeostatic balance in the human body and can lead to toxicity. Human Mn deficiency has been reported in patients on parenteral nutrition and in micronutrient studies. Mn toxicity has been reported through occupational (e.g. welder) and dietary overexposure and is evidenced primarily in the central nervous system, although lung, cardiac, liver, reproductive and fetal toxicity have been noted. Mn neurotoxicity results from an accumulation of the metal in brain tissue and results in a progressive disorder of the extrapyramidal system which is similar to PD. Chelation therapy with EDTA and supplementation with levodopa are the current treatment options, which are mildly and transiently efficacious. Repeated administration of Mn, or compounds that readily release Mn, may increase the risk of Mn-induced toxicity [34].

Conclusion

The review article has highlighted the research findings during the past two decades on the role of Mn in human health and disease. Many research findings have been done on laboratory animals and some in humans. Lacunae still exists in this field especially studies in India. Mn plays a highly significant role in carbohydrate metabolism and shows its ettect on liver, cardiac, kidney CNS and other physiological regulating functions. While Mn deficiency leads to poor diabetic controls as well as liver and cardiac activities, excess may lead to neurological damages, significant deposition in

some organs. PD is said to be linked to over consumption of Mn in diets. More research are required in this field on humans especially on diabetes, Kidney and liver disorders and to arrive at an optimal supplementation dosage.

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