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The role of manganese in etiopathogenesis and prevention of selected diseases

Rola manganu w etiopatogenezie i prewencji wybranych schorzeń

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Summary

Manganese (Mn) is an essential trace element, necessary for development and growth of the organism. The adequate content of this element in the body determines proper metabolism of amino acids, cholesterol and carbohydrates. This mineral influences activity of several enzymes involved in metabolic and redox processes. Mn absorption and retention disturbances may participate in etiopathogenesis of some diseases and disorders.

This article is a review of knowledge about the role of Mn in etiopathogenesis and prevention of selected diseases: brain disorders, diabetes, lipid disturbances and cancers.

Key words: **manganese • diabetes • brain disorders • cancer**

Streszczenie

Mangan (Mn) należy do pierwiastków śladowych, niezbędnych do prawidłowego rozwoju i wzrostu organizmu. Podaż tego składnika mineralnego zgodna z zapotrzebowaniem organizmu determinuje prawidłowy metabolizm większości składników odżywczych m.in.: aminokwasów, cholesterolu i węglowodanów. Wynika to m.in. z tego, że pierwiastek ten wpływa na aktywność wielu enzymów, uczestniczących w przemianach metabolicznych oraz w procesach redox organizmu. Nieprawidłowa podaż Mn bądź zaburzone procesy absorpcji i/lub retencji mogą się przyczynić do rozwoju niektórych schorzeń.

W artykule przedstawiono aktualny przegląd piśmiennictwa dotyczący roli Mn w etiopatogenezie i prewencji wybranych schorzeń: zaburzeń funkcjonowania OUN, cukrzycy, zaburzeń przemiany tłuszczów, a także nowotworów.

Słowa kluczowe: **mangan • cukrzyca • nowotwory**

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Introduction

Manganese (Mn) as a cofactor of several enzymes involved in metabolic processes and of manganese superoxide dismutase (MnSOD) is a trace element necessary for the proper development and growth of the organism [4]. MnSOD and others from the SOD enzyme family – copper--zinc superoxide dismutase (Cu-Zn-SOD)) and extracellular superoxide dismutase – catalyze dismutation of superoxide anion to hydrogen peroxide and molecular oxygen. This element is also involved in bone formation and metabolism of amino acids, cholesterol and carbohydrates [5]. The proper content of this element is essential for normal body growth and functioning. Mn deficiency is not usually observed in humans but some studies performed with animals showed that insufficient intake of this mineral can lead to: skeletal abnormalities, decreased glycosyltransferase activity, impaired reproductive function in females and testicular degeneration in males [13]. Excessive intake of manganese can have toxic effects – manifested by impaired redox potential and changes in activity of the central nervous system (CNS) [13,23,25,36]. Negative health effects of elevated Mn concentration in tissue are mainly determined by workplaces where pollutant production is uncontrolled and workers are continuously exposed to high levels of manganese [29]. Exposure to airborne Mn oxide has been reported in miners, workers in dry-cell battery factories, smelters, and welders. Mn as a bactericidal and fungicide agents is used in water purification and as an antiknock agent in gasoline [17].

There are many studies concerning Mn toxic effects especially on brain functioning [6,19,22,23]. Still little is known about the role of Mn in prevention and etiopathogenesis of other disorders. The authors of this review focused on the following diseases: diabetes, lipid disorders, brain disorders and cancers.

Absorption and metabolism of Mn

The typical range of Mn in mammalian tissue concentration is 0.3–2.9 μg Mn/g wet tissue with the highest accumulation in brain, bone, pancreas, liver, kidney and high pigment content tissue e.g. retina [4]. Daily intake of manganese by humans is in the range of approximately 5–12 mg/d and 2–5 mg Mn is considered to be a safe and adequate daily intake for adults [4,17].

Approximately 1–5% of the daily Mn supply is absorbed from the intestinal lumen [4]. Several dietary factors may affect Mn absorption, e.g. dietary iron, presence of phytate and type of fat [8,12,15,39]. Dietary iron and the whole-body retention of this mineral has a great impact on Mn absorption from the lumen. Transport and homeostasis of Fe and Mn are connected. The cellular Mn (III) uptake system is mediated by the transferrin receptor mediated Fe uptake system, which has higher affinity for Fe (III). Also divalent Mn transport and homeostasis are linked to Fe (II) transport and homeostasis. Divalent metal transporter 1 (DMT1) transports Fe (II) and Mn (II) and is controlled by cellular Fe status [39].

There is also a negative correlation between content of Mn in diet and absorption of this trace element. Finley et al. [15] demonstrated that women who consumed a diet with low content of Mn (0.8 mg/d) absorbed a higher percentage of this mineral compared to women who consumed a diet with high content of Mn (20 mg/d). The women with low Mn diet also had a significantly longer biological half-life of absorbed Mn than subjects with high Mn diet – 22.5 d *vs* 11.9 d. This study confirmed that absorption and retention of this mineral are also strongly regulated by Mn consumption, which is the result of a compensatory mechanism.

The impact of individual fatty acid types and amount on Mn absorption from the gastrointestinal tract is ambiguous. Finley et al. [12] revealed significantly higher Mn accumulation and longer retention in rats fed a diet high in polyunsaturated fatty acids (PUFAs) compared to rats fed a diet high in saturated fatty acids (SFAs). Next Finley's study performed on humans showed that type of fat did not affect the percentage of Mn absorption, but the Mn retention was significantly greater in women fed a high SFA diet compared to a PUFA diet. In this research with a crossover design healthy young women were fed diets providing 0.8 or 20 mg Mn per day. One half of women received 15% of energy from SATs as cocoa butter and one half received – 15% of energy from PUFAs as corn oil [15]. It is difficult to explain the role of dietary fat type on Mn absorption and retention, especially because of different results in animal and human studies. More research is needed to explain this issue.

Gender can impact on Mn absorption and retention. Finley et al. [14] demonstrated statistically higher percentage of Mn absorbed by women than men but the male retention of this mineral was longer than female. The authors suggested that iron status could affect manganese absorption and retention, which was confirmed in Finley's next study [11]. The authors also revealed a negative correlation between Mn absorption and serum ferritin concentration and between Mn absorption and Mn biological half-life [11]. The results of these studies also confirmed that iron status, demonstrated by ferritin concentration, very strongly influences Mn absorption.

Elimination of manganese occurs mainly through the bile duct (~80%). Liver's disturbances (advanced cirrhosis due to e.g. alcoholic liver disease or primary biliary cirrhosis) may affect manganese elimination, which can result in elevated blood Mn concentration. Total parenteral nutrition which avoids gut and liver control mechanisms may also be a cause of Mn accumulation [37].

The role of Mn in etiopathogenesis and prevention of diabetes

According to the WHO definition diabetes mellitus is a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs [32]. Oxidative stress is one of the key factors influencing development of diabetes and its complications [20]. Proper intake of dietary antioxidants may protect against the development of this disease. There are many reports about such activity of antioxidant vitamins

[9,18] and some minerals like magnesium, calcium, and zinc [31,33,41]. Still little is known about the role of manganese in etiopathogenesis and prevention in diabetes.

In the scientific literature there are results of studies concerning Mn in connection with diabetes, but they are ambiguous. Kazi et al. [21] and Afridi et al. [2] determined the content of Mn in hair and whole blood of patients with type II diabetes, diabetic mothers, their offspring and healthy subjects and found lower values in the group of patients compared to healthy people. Adewuni et al. [1] revealed significantly lowered serum concentration of Mn in diabetic patients compared to the control group. They also observed lowered mean concentration of chromium and copper in diabetic patients sera. The authors reported that 75% of recruited patients had trace element deficiencies which could predispose to oxidative stress and diabetes development. On the other hand Anetor et al. [3], and Flores et al. [16] demonstrated that mean serum Mn concentration in patients with type II diabetes was significantly higher than in the control group Ekmekcioglu et al. [10] also found higher mean Mn serum concentrations in diabetic patients than in the control group, but the difference was not statistically significant. However the authors demonstrated statistically significantly lower levels of this element in the lymphocytes of patients compared with the control group.

Finley et al. [15] assessed the impact of dietary Mn on the clinical measures in healthy young women. The plasma glucose, insulin and area under curve after an intravenous glucose tolerance test were not influenced by content of Mn in diet (0.8 mg Mn *vs* 20 mg Mn). Information from studies concerning the role of Mn in diabetes etiology is not consistent, therefore more research is needed to understand it.

The role of Mn in lipid metabolism disorders

There are some studies demonstrating a link between serum Mn concentration or dietary Mn and lipid metabolism but these data are incomplete or conflicting. Sands et al. [34] evaluated the effect of dietary manganese supplementation on chicken lipid metabolism. The authors noted a significantly lower mean serum concentration of free fatty acids in chickens whose diets were enriched in Mn compared with the control group fed a standard diet. There were no significant differences in the concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides determined in the sera of chickens fed a standard diet and a diet with increased quantities of Mn. On the other hand in the study by Finley et al. [15] in humans, subjects who consumed a diet with low Mn content (0.8 mg Mn/d) had significantly lower very low-density lipoprotein (VLDL) cholesterol concentration compared to subjects fed a high Mn diet (20 mg/d), respectively 0.56 mmol/l and 0.61 mmol/l ($p<0.02$).

Lu et al. [24] demonstrated statistically lower percentages of abdominal fat and also lipoprotein lipase and malate dehydrogenase activities in chicken supplemented Mn than in birds fed a control diet. The authors also revealed a statistically lower malondialdehyde level in leg muscle and higher activity of MnSOD and concentration of MnSOD mRNA in leg muscle and breast of Mn supplemented chicken than control birds. The authors suggested that Mn supplementation of diet may reduce abdominal adipose deposition.

The role of Mn in neurological disorders

Chronic exposure to Mn causes a neurological disorder called manganism, manifesting psychiatric, cognitive and motor disturbances [17]. It provokes the neurodegenerative disturbances mainly in basal ganglia characterized by gliosis and expression of enzyme genes including nitric oxide synthase (NOS2). Excessive synthesis of NO causes neuronal cell failure which is associated with Parkinsonism-like motor deficits [28]. In a study determining the mechanisms of neural stem cell death when exposed to manganese, Tamm et al. [36] revealed manganese toxicity due to reactive oxygen species (ROS) formation. The incubation of C17.2 cell line in $MnCl_2$ (doses ranging from 50 to 250 μM for 12, 18, 24, 48 h) resulted in time- and dose-dependent manner nuclei condensation. The authors found the activation of proapoptotic protein Bax, increased activity of caspases-3 and mitochondrial cytochrome c release which suggested that cell death occurred through apoptosis.

In the Klos et al. [22] study, 15 patients with liver failure and basal ganglia T1 hyperintensity on magnetic resonance imaging (MRI) were recruited. Three syndromes were recognized: parkinsonism (n=9), gait ataxia plus other neurological findings (n=3) and cognitive impairment with psychiatric disturbances (n=3). All patients except one had elevated blood Mn concentration. The authors suggested that Mn brain accumulation demonstrated by basal ganglia T1 hyperintensity on MRI could be the main component of neurological disturbances caused by liver failure.

The possible role of Mn in cancer development

Mn is a cofactor of antioxidant enzymes including MnSOD which is the fundamental mitochondrial enzyme that scavenges ROS [27]. The activity of this enzyme can prevent cancer development. In the Chen et al. [7] study, the use of recombinant human MnSOD against mice with implanted solid tumors induced by Sarcoma 180 cells inhibited tumor expansion in a dose-dependent manner. The authors also revealed positive enhancement the numbers of CD-4 and CD-8 cells which suggests that recombinant MnSOD increases the activity of the immune system. Remmen et al. [38] studied the impact of MnSOD activity on total cancer incidence. The authors demonstrated 100% increase of tumor incidence (the number of mice with tumors) in $Sod2^{+/-}$ mice with reduced MnSOD activity (~50%) compared to wild type mice.

The statistical differentiation of serum levels of Mn in normal, benign and malignant breast cancer patients was observed in the Wu et al. study [40]. The authors demonstrated statistically higher Mn serum concentration in the healthy than the benign group (9.09 μg/l *vs* 7.47 μg/l) and in the healthy than the malignant group (9.09 μg/l *vs* 5.50 μg/l). On the other hand, Pasha et al. [30] revealed that mean concentration of Mn in scalp hair of different cancer patients was statistically higher than in normal donors. In the Milde et al. study [26] the mean serum Mn concentrations of adenocarcinoma colorectal cancer patients was also significantly higher than in the control group. The impact

of Mn in cancer development depends on several factors: the kind of Mn compounds (organic or inorganic), concentration of Mn in the environment and in the organism, and also on the kind of Mn pollution [17].

Mn plays an important role in antioxidant defenses so it can prevent cancer development. On the other hand Mn compounds can induce mutations in Escherichia coli and Saccharomyces cerevisiae [17]. Although there are reports indicating Mn mutagenicity, still little is known about Mn-induced cancers. In the Spangler et al. study [35] groundwater manganese was positively correlated with total cancer, colon cancer, and lung cancer North Carolina death rates. By contrast airborne manganese was negatively associated with total cancer, breast cancer and lung cancer death rates. The data about Mn carcinogenicity are ambiguous so more research is needed to solve this problem.

Conclusions

Many studies have been performed concerning this mineral but still too little attention has been paid to recognizing biological functions of this transition metal taking into account its necessity for the human body. This element is regarded primarily as a toxin responsible for manganism. There are not many papers concerning the role of manganese in etiopathogenesis and prevention of diseases, therefore there is a gap in knowledge about its impact on human body functioning. Further research is needed to explain at the cellular level the role of Mn in some disturbances and diseases.

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