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Sex, pregnancy, and age-specific differences of blood manganese levels in relation to iron status; what does it mean?

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ABSTRACT

The objective of the present study was to evaluate sex, menopause, pregnancy, and age-specific differences of blood manganese (Mn) levels in relation to iron status, and to assess the toxicological implications of these relationships. Females of childbearing age have higher concentrations of blood Mn than males because women have lower concentrations of ferritin. Previous studies indicated significant increases in blood Mn levels throughout pregnancy, and that the geometric mean of blood Mn was significantly higher in premenopausal women than postmenopausal women. This may be due to the enhanced absorption of Mn because of upregulation of iron absorption, which is especially important during late pregnancy. Mn concentrations are highest in infancy, decreased with age up to adolescence, and did not change during adulthood. Thus, the relationship of iron with Mn may be the major factor affecting blood Mn levels according to menstrual stage, reproductive status, menopausal factors, and age. However, Mn absorbed *via* the gastrointestinal system seems to be less neurotoxic than inhaled or parenteral Mn, due to the tight enterohepatic homeostatic control of this essential element. Furthermore, children and pregnant women had no adverse health effects from blood levels of Mn that were associated with adverse effects in adult workers. In conclusion, the differences between a physiological and a pathological hypermanganesemia complicate interpretation of the dose-response relationship.

1. Background

Manganese (Mn) is a substance with a dual role in organism. Mn is an essential trace element that is required for maintaining proper function and regulation of numerous biochemical and cellular reactions. Despite its essentiality, at excessive concentrations Mn is highly toxic to the central nervous system [29,33]. Animal studies demonstrated that intestinal absorption of Mn is markedly greater under conditions of iron deficiency. The gastrointestinal absorption of Mn appears to require intestinal iron transporters, such as apical divalent metal transporter 1 (DMT1), which also mediates the uptake of cadmium. DMT1 expression is greater in the presence of low iron stores, and this explains the increased Mn uptake and blood Mn under conditions of iron deficiency [7,11,15,16,22,25]. Emerging new evidence indicates that the iron exporter ferroportin also transports Mn [12,24].

Females of childbearing age have higher concentrations of blood Mn than males because women have lower concentrations of ferritin [19]. Premenopausal women have a higher geometric mean (GM) concentration of blood Mn than postmenopausal women. Increased ferritin may not affect blood Mn levels at menopause, because DMT1 may be inactivated at this time [23]. Previous studies consistently reported significant increases in the mean blood Mn levels throughout pregnancy [34–36]. Rükgauer [32] showed that serum Mn concentration was highest during infancy, decreased with age up to adolescence, and did not change during adulthood.

The objective of the present study was to evaluate sex, menopause, pregnancy, and age-specific differences of blood Mn levels in relation to iron status, and to assess the toxicological implications of these findings. A literature review was performed on relevant articles and their references in the field of toxicity, physiology, and toxicology of Mn using PubMed from 1965 until 2016.

2. Sex, menopause, pregnancy, and age-specific differences of blood Mn levels in relation to iron status

2.1. Sex

My previous study showed that females of childbearing age had higher concentrations of blood Mn than males in general population [23] and residents with environmental exposure to Mn [20], in agreement with other studies [2,16,25,27] (Table 1). DMT1 expression is greater in the presence of low iron stores, and this may explain the

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Table 1
Studies that examined the effect of sex, menopause, pregnancy, and age on blood Mn concentration.

Variables	No. (n)	Study subjects and findings
Sex	(n = 2005)	Korean general population 20 y or more; KNHANES 2008/GM of blood Mn in female vs. male: 1.403 vs. 1.192 μg/dL* [19]
	(n = 297)	Canadian general population/GM of blood Mn in female vs. male: 0.750 vs. 0.675 μg/dL* [2]
	(n = 7720)	USA general population (NHANES 2010-11)/GM of blood Mn in female vs. male: 0.99 vs. 0.87 μg/dL* [27]
Menopause	(n = 1826)	Korean general population KNHANES 2008–2009/GM of blood Mn in pre- vs. post-menopause: 1.443 vs. 1.296 μg/dL* [23]
Pregnancy	(n = 34)	Australian general population/Maternal blood Mn during pregnancy from 10 to 20 wk vs. 25 vs. 34 wk; 0.82 vs. 0.94 vs. 1.26 μg/dL [34]
	(n = 290)	Canadian general population/Maternal blood GM Mn during pregnancy at 3rd, vs. 2nd, vs. 1 st trimester vs. non-pregnant 1.56 vs. 0.95 vs. 0.85 and 0.746 μg/dL [35]
	(n = 66)	Swedish general population/Maternal blood median Mn during pregnancy at 3rd, vs. 2nd, vs. 1 st trimester 1.26 vs. 1.04 vs. 0.85 μg/dL [36]
	(n = 470)	Canadian general population/Maternal blood AM Mn during pregnancy at delivery vs. non-pregnant; 2.4 vs. (0.8–1.2) μg/dL [37]
	(n = 1085)	USA general population/blood GM Mn in pregnancy vs. non-pregnant; 1.19 vs. 1.02 μg/dL [27]
	(n = 265)	Korean general population/blood GM Mn in pregnancy; 2.25 μg/dL [8]
Age	(n = 2005)	Korean general population 20 y or more; KNHANES 2008/No significant change between 20′s and 40′s [19]
	(n = 7720)	US general population/blood GM Mn in age groups (1–5 years-old: 1.07 μg/dL; 6–11 years-old: 1.03 μg/dL; 12–19 years-old: 1.01 μg/dL; 20+ years-old: 0.91 μg/dL) [4]
	(n = 205)	German population/serum mean Mn in age groups (1, 4–6, 10–14, 22–75): 0.21, 0.14, 0.12, 0.08 μg/dL) [32]

GM, geometric mean; KNHANES, Korea National Health and Nutrition Examination Survey; NHANES, National Health and Nutrition Examination Survey. * Statistically significant.

increased Mn uptake and blood Mn levels of females, because females of childbearing age have lower concentrations of ferritin than males [7,11,15,16,22,25].

2.2. Menopause

Previous research showed that premenopausal women had a significantly higher GM of blood Mn than postmenopausal women (1.436 *vs.* 1.30 μg/dL) in general population [23] (Table 1) and residents with environmental exposure to Mn [20]. Increased ferritin may not affect Mn levels during menopause, because DMT1 may be inactivated at this time. Multivariable linear regression analyses showed that serum ferritin and menopausal status were significant predictors of blood Mn (after adjusting for various covariates), and that menopausal status modified the effect of ferritin on blood Mn levels [23].

2.3. Pregnancy

Previous studies consistently reported significant increases in the mean blood Mn levels throughout pregnancy [34–36] (Table 1). This increase in blood Mn may be related to the enhanced absorption of Mn due to upregulation of iron absorption, particularly during late pregnancy [3,21], because more iron is needed during the third trimester.

2.4. Age

Rükgauer [32] showed that serum Mn concentration was highest during infancy, decreased with age up to adolescence, and did not change during adulthood. A study of the general population in the United States also showed that the GM blood Mn level decreased with age (1–5 years-old: 1.07 μg/dL; 6–11 years-old: 1.03 μg/dL; 12–19 years-old: 1.01 μg/dL; 20+ years-old: 0.91 μg/dL) [4] (Table 1). In agreement, my research reported no age-related changes in blood Mn of individuals from their 20′s to 40′s [19], because homeostatic mechanisms control the absorption, deposition, and biliary excretion of this essential element. My previous study found that infants with iron deficiencies had a higher mean blood Mn concentration than controls (2.550 *vs.* 1.499 μg/dL), and that administration of iron therapy to iron-deficient infants significantly decreased their blood Mn levels, and significantly increased their hemoglobin and ferritin levels [28]. Interestingly, the mean blood Mn level in the control group of infants from this previous study (1.499 μg/dL) was higher than the reference value (1.215 μg/dL) reported for the general adult population of Korea [19] and the normal reference range (0.4–1.4 μg/dL) by the Agency for Toxic Substances and Disease Registry (ATSDR) [1]. Dorner et al. [13] showed that infants, especially premature infants, have higher levels of Mn than adults. Animal studies showed that absorption and/or retention of Mn is greater in neonates, but returns to the level of older animals at approximately post-gestational day 17–18 [30]. Mn requirements vary by life stage, and infants typically have higher levels than children or adults [31]. This is mainly due to the high need for iron and the concurrent absorption of Mn in infants, who experience rapid growth, and often suffer from inadequate intake of dietary iron between 6 months and 3 years of age [28].

In summary, the relationship of iron with Mn may be the major factor affecting changes in blood Mn due to menstrual stage, reproductive status, menopausal factors, and age in general population and residents with environmental exposure to Mn. However, whether negative associations between blood Mn concentration and low serum ferritin levels are observed in workers with occupational exposure, and their temporal relationship are not yet determined [14,10].

3. Physiologic *vs.* pathologic hypermanganesemia

My previous study showed that patients with iron-deficiency anemia had higher blood Mn concentrations than controls (2.04 μg/dL *vs.* 1.28 μg/dL) [18]. However, the mean pallidal index (PI) in anemic patients was similar to that of controls, and neither group had high signal intensity of the globus pallidus in T1-weighted MRI. This finding is in contrast to those of my previous study of males with liver cirrhosis. In this cirrhosis study, we observed a significantly increased PI in 27 of 33 patients (81.8%) with liver cirrhosis (mean blood Mn concentration: 2.34 μg/dL) relative to controls without cirrhosis (mean blood Mn concentration: 1.44 μg/dL) [6]. Similarly, 18.6% of welders exposed to Mn (mean blood Mn: 1.53 μg/dL) had an increased PI, and the mean PI in welders was significantly different from that of controls (mean blood Mn: 1.14 μg/dL) ($p < 0.001$) [5]. Thus, although intestinal absorption of Mn is greater in patients with iron-deficiency anemia, MRI signal intensity in the globus pallidus is minimally affected, in contrast to individuals with liver cirrhosis or occupational Mn exposure. These findings are consistent with those of Newland et al. [26], who studied Mn toxicity in long-tailed macaques. They found that parenteral exposure increased the Mn concentration in the basal ganglia, and this led to a higher PI, but oral exposure did not increase Mn concentration in the brain and did not increase the PI. Mena et al. [25] showed that increased Mn excretion ameliorated the increased Mn absorbed due to anemia, thereby preventing toxic effects. Taken together, normal physiologic Mn exposure *via* intestinal absorption seems to be less neurotoxic than parenteral or inhaled Mn, due to the tight enterohepatic homeostatic control of this essential element.

Blood Mn levels in children and pregnant women are higher than in adults. In particular, the mean blood Mn level (1.499 μg/dL) of control infants was higher than the reference value (1.215 μg/dL) for the general adult population of Korea [19] and was also higher than control adults [5,6,18] of my previous studies. A study of the general population in the United States also showed that the GM blood Mn level decreased with age [4]. Data on pregnant women indicated that blood Mn levels at delivery was at least 1.5-2 times higher than that of non-pregnant women and women in early pregnancy [8,34–36].

The blood Mn concentrations that are typical in children and pregnant women (from oral or non-occupational exposures) are similar to the critical concentrations reported for welders exposed to Mn, who have at most 1.5-fold higher blood Mn levels than controls, and also have poor neurobehavioral performance, and higher PI scores [5,17]. Claus Henn et al. [9] reported an inverted U-shape relationship between blood Mn (mean: 2.43 μg/dL, SD: 4.5) and neurodevelopment in 12 month olds, in that Mn deficiency (1.5-2.0 μg/dL) and Mn excess (more than 3.0 μg/dL) were associated with lower scores. Chung et al. [8] suggested an inverted U-shaped relation between maternal blood Mn at term and neurodevelopmental indexes of infants 6 months after birth. They found that maternal blood Mn concentration up to approximately 2.4–2.8 μg/dL was positively associated with 6-month psychomotor development index (PDI) score, but higher maternal blood Mn concentration was associated with a lower PDI score, suggesting adverse neurodevelopmental effects of low levels (< 2.0 μg/dL) and high levels (≥ 3.0 μg/dL) of maternal blood Mn. The results of these 2 studies of non-occupational exposure to Mn may seem perplexing, because blood Mn levels indicative of normal physiologic concentration in infants and pregnant women would be considered over threshold levels in adult workers. In other words, children and pregnant women do not exhibit adverse health effects when they have blood Mn levels associated with toxicity in adult workers. Taken together, these results suggest that the route or mechanism of exposure to Mn is more important than the blood Mn concentration.

The presence of different blood Mn levels in healthy subjects of different age, sex, and pregnancy and menopausal status makes it difficult to compare findings among studies, especially those related to dose-effect relationships. The differences between a physiological and a pathological hypermanganesemia, further complicates interpretation of the dose-response relationship. Thus, the interpretation of pathogenic values should be based on normal levels or threshold concentrations in different groups of study subjects while taking into account the pathway of Mn into the organism. Details of the dose-response relationships in different study subjects remain to be clarified.

Disclosure

The authors have no potential conflicts of interest to disclose.

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