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Review Article

Sex-specific Profiles of Blood Metal Levels Associated with Metal–Iron Interactions

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ABSTRACT

The mechanisms by which iron is absorbed are similar to those of divalent metals, particularly manganese, lead, and cadmium. These metals, however, show different toxicokinetics in relation to menarche or menopause, although their interaction with iron is the same. This review focuses on the kinetics of these three toxic metals (manganese, lead, and cadmium) in relation to menarche, pregnancy, and menopause. The iron–manganese interaction is the major factor determining sex-specific differences in blood manganese levels throughout the whole life cycle. The effects of estrogen overshadow the association between iron deficiency and increased blood lead concentrations, explaining why women, despite having lower ferritin concentrations, have lower blood lead concentrations than men. Iron deficiency is associated with elevated cadmium levels in premenopausal women, but not in postmenopausal women or men; these findings indicate that sex-specific differences in cadmium levels at older ages are not due to iron–cadmium interactions, and that further studies are required to identify the source of these differences. In summary, the potential causes of sex-specific differences in the blood levels of manganese, lead, and cadmium differ from each other, although all these three metals are associated with iron deficiency. Therefore, other factors such as estrogen effects, or absorption rate as well as iron deficiency, should be considered when addressing environmental exposure to toxic metals and sex-specific differences in the blood levels of these metals.

1. Introduction

Toxic metals have become ubiquitous in the built environment, and thus the general populations are increasingly becoming exposed to these metals. Most research in toxicology and environmental and occupational health has only involved men. However, increasing evidence suggests that the toxicity of environmental pollutants, including toxic metals, may manifest differently in women than in men. Although many epidemiological studies have reported data separately for men and women, differences between the genders have seldom been evaluated [1–3]. Moreover, little is known about toxicity in relation to specific periods in women's lives, such as menarche and menopause. Menstruation may cause iron deficiency, which, in turn, may be related to increased gastrointestinal absorption of toxic metals [4,5]. Mechanisms of iron absorption are similar to those of other divalent metals, particularly manganese, lead, and cadmium [4,5] and a dietary deficiency of iron can lead to excess absorption of manganese [6–13], lead [14–23], and cadmium [24–29].

Metal ions show different toxicokinetics in relation to menarche, pregnancy, or menopause, despite similar metal–iron interactions. Thus, this review focuses on the kinetics of the toxic metals with a similar metal–iron interaction, such as manganese, lead, and cadmium, in relation to menarche, pregnancy, and menopause in the general population without occupational exposure.

2. Manganese

Manganese is a naturally occurring element that is abundantly present in the environment. It is an essential dietary nutrient needed for proper functioning of the human body at specific concentrations. It plays a role in bone formation, protein and energy

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metabolism, and metabolic regulation, and functions as a cofactor in a number of enzymatic reactions [30]. Because manganese is an essential element [30–32], its absorption, disposition, and biliary excretion are actively controlled by homeostatic mechanisms [30,33]. These processes also play an important role in manganese toxicokinetics, which differ from those of nonessential toxic metals such as lead and cadmium. Heavy occupational exposure to manganese can cause a neurologic impairment clinically called "manganism," a motor syndrome that is similar to but differentiated from idiopathic Parkinson's disease [33–37]. The mechanisms involved in iron absorption are similar to those of divalent metals, particularly manganese [4,27], and a dietary deficiency of iron can lead to excess absorption of manganese [6–13]. Higher concentrations of blood manganese are reported in females of childbearing age than in males because the former have lower concentrations of ferritin [11,12,38]. Moreover, blood manganese levels are lower in menopausal than in premenopausal women because the former have higher concentrations of ferritin [39]. Significant increases in the mean whole blood manganese levels throughout the pregnancy period were reported previously [32,40,41]. This increase in manganese levels may be related to the enhanced absorption of manganese due to upregulation of iron absorption, particularly during the late pregnancy periods [42,43], because mechanisms of iron absorption are similar to those of other divalent metals, particularly manganese and cadmium [4,5]. However, age-related increase in blood manganese is not observed [11], because its absorption, disposition, and biliary excretion are actively controlled by homeostatic mechanisms as an essential element [30]. Thus, the iron–manganese interaction is the major factor determining sex-specific differences in blood manganese levels in relation to menstrual, reproductive, and menopausal factors (Table 1) [11,32,38–41].

3. Lead

Lead is a widespread environmental pollutant that can damage the central nervous, renal, cardiovascular, reproductive, and hematological systems. Lead accumulated in bones has a half-life ranging from years (trabecular bone) to decades (cortical bone) [44]. Approximately 90% of the lead in the body is stored in the skeleton [45].

Because iron is absorbed by mechanisms similar to those of other divalent metal ions, including lead and manganese, a dietary deficiency of iron can lead to excess absorption of lead [46–48]. Several studies have suggested an association between iron status and blood lead concentration in children [14–23] and in premenarchal females [49]. However, the relationship between iron deficiency and increased lead absorption has not been widely reported in adults [50,51]. Despite having lower ferritin levels, postmenarchal females have lower blood lead concentrations than males of similar ages [49,52–56]. Furthermore, blood lead concentrations are higher in menopausal than in premenopausal women, despite the former having higher ferritin levels. Our previous study [49] suggested that these paradoxical findings are probably due to the potential confounding effect of estrogen on blood lead levels. Several studies have shown that blood lead concentrations are higher in menopausal than in menstruating women, because lead may be mobilized from the skeleton during periods of increased bone demineralization, such as in menopause [57–62]. In addition, lower blood lead levels were observed in postmenopausal women receiving estrogen replacement therapy than in past or never users [63–65]. The National Health and Nutrition Examination Survey data showed that blood lead levels were lower among girls who had attained sexual maturity [66]. Estrogen triggers rapid bone formation during pubertal development, inducing more rapid deposition of calcium, as well as lead, from blood into bone and possibly causing redistribution of lead throughout the body. These findings indicate that the effects of estrogen overshadow the association between iron deficiency and increased blood lead levels, and explain why women, despite having lower ferritin levels, have lower blood lead levels than men. These sex-specific differences in blood levels of lead between men and women were reported previously [53,67]. In addition, Wu et al [66] found a significant difference in blood lead concentration between Chinese male and female children aged 7–14 years (5.072 μg/dL vs. 4.389 μg/dL), but not in children aged <7 years. Our previous report also did not show a significant sex-specific difference in blood lead concentration between premenarchal girls and boys [49]. There was also a significant decrease in the mean whole blood lead levels throughout the pregnancy period [68–71] although some recovery is also seen in the late stages of pregnancy in some studies [70,72,73]. This decrease during pregnancy may be mainly related to physiological factors, such as increases in plasma estrogen concentrations and their effect on lead redistribution. Thus, the decreasing effect of estrogen on blood lead is a major determinant of sex-specific differences in blood lead levels as a common thread relating menstrual, reproductive, and menopausal factors (Table 2) [40,49,53,57,58,61,62,67–71,74,75]. However, age-related increase in blood lead is observed because of increase in exposure with age [67,74].

4. Cadmium

Cadmium is a ubiquitous environmental pollutant with a biological half-life in the body exceeding 10 years. Cadmium levels in the body accumulate with age, as only a minute part (0.01–0.02%) is excreted per day [76]. Cadmium has been reported to have cumulative effects on mortality and cardiovascular, neurologic, renal, and developmental diseases [76].

Blood cadmium is a valid biomarker of recent cadmium exposure [77], whereas urinary cadmium is a biomarker of lifetime exposure to cadmium [77]. Iron and cadmium have similar

Table 1
Behavior of blood manganese (Mn) concentrations according to age- and sex-related variables

Variables	Refs (*n*)	Study populations and findings
Age	[11] (2,005)	Korean general population aged ≥20 y; KNHANES 2008/No significant change between population in the 20s and 40s
Sex	[11] (2,005)	Korean general population aged ≥20 y; KNHANES 2008/GM of blood Mn in females vs. males: 1.403 μg/dL vs. 1.192 μg/dL*
	[38] (297)	Canadian general population/GM of blood Mn in females vs. males: 0.750 μg/dL vs. 0.675 μg/dL*
Menopause	[39] (1,826)	Korean general population KNHANES 2008–2009/GM of blood Mn in premenopausal vs. postmenopausal women: 1.443 μg/dL vs. 1.296 μg/dL*
Pregnancy	[32] (34)	Australian general population/maternal blood Mn during pregnancy from 10 wks to 20 wks vs. 34 wks: 0.375 μg/dL vs. 0.575 μg/dL
	[40] (290)	Canadian general population/maternal blood GM of Mn during pregnancy at delivery vs. 1st trimester and nonpregnant women: 1.56 μg/dL vs. 0.85 μg/dL and 0.746 μg/dL
	[41] (470)	Canadian general population/maternal blood AM of Mn during pregnancy at delivery vs. nonpregnant 2.4 μg/dL vs. 0.8–1.2 μg/dL

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

Table 2
Behavior of blood lead concentrations according to age- and sex-related variables

Variables	Refs (*n*)	Study populations and findings
Age	[67] (9,961)	U.S. general population; NHANES 1999–2002/significant increase with age
	[74] (5,924)	Korean general population aged ≥20 y; KNHANES 2008–2010/significant increase with age
Sex	[67] (9,961)	U.S. general population; NHANES 1999–2002/GM of blood lead in men vs. women: 2.08 μg/dL vs. 1.31 μg/dL
	[53] (8,793)	U.S. general population; NHANES 2009–2010/GM of blood lead in men vs. women: 1.31 μg/dL vs. 0.966 μg/dL
	[74] (5,924)	Korean general population aged ≥20 y; KNHANES 2008–2010/GM of blood lead in men vs. women: 2.620 μg/dL vs. 2.008 μg/dL*
	[75] (3,181)	Children aged 0–14 y from Beijing, China/AM of blood lead in male children vs. female children aged 7–14 y: 5.072 μg/dL vs. 4.389 μg/dL, but no differences in children aged <7 y
	[49] (798)	Korean general adolescent population; KNHANES 2010–2011/GM of blood lead in premenarchal girls vs. boys: 1.403 μg/dL* vs. 1.497 μg/dL
Menarche	[40] (396)	Korean general adolescent population; KNHANES 2010–2011/GM of blood lead in premenarchal vs. postmenarchal girls: 1.403 μg/dL vs. 1.136 μg/dL*
Menopause	[61] (745)	Korean general population; KNHANES 2008–2009/blood GM of lead in premenopausal vs. postmenopausal women: 2.0 μg/dL vs. 2.274 μg/dL*
	[57] (846)	U.S. general population; NHANES 1976–1980/blood GM of lead in premenopausal vs. postmenopausal women aged 40–60 y: 11.63 μg/dL vs. 13.09 μg/dL*
	[58] (3,136)	U.S. general population; NHANES 1982–1984/blood GM of lead in premenopausal vs. postmenopausal women: 7.5 μg/dL vs. 8.9 μg/dL*
	[62] (3,221)	U.S. general population; NHANES 1999–2010/blood GM of lead in premenopausal vs. postmenopausal women aged 45–55 y: 1.23 μg/dL vs. 1.71 μg/dL*
Pregnancy	[68] (26,570)	U.S. general population; NHANES 2003–2008/blood GM of lead among pregnant women aged 18–49 y vs. nonpregnant women: 0.64 μg/dL vs. 0.85 μg/dL*
	[69] (128 vs. 120)	Chinese general population (Chengdu)/blood AM of 3 trimesters vs. healthy control group: 5.957 μg/dL, 5.517 μg/dL, and 5.577 μg/dL vs. 6.87 μg/dL*
	[71] (165 vs. 27)	UK general population/blood AM of lead levels of pregnant vs. nonpregnant women: 12.22 μg/dL vs. 13.25 μg/dL (insignificant)
	[70] (12)	Australian immigrants/changes in blood GM of lead during pregnancy and postpartum followed U-shaped patterns

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

absorption mechanisms [4,27], and animal experiments have shown that metabolic interactions may take place between cadmium and iron [78,79]. Increased cadmium uptake in animals with low iron stores has been documented previously [24,25,28,29]. Moreover, cadmium concentrations were shown to be associated with decreasing iron stores in premenopausal women [1,12,52,80–85]. Thus, blood cadmium concentrations are higher in females of childbearing age than in males because the former have lower ferritin concentrations [53,74,86,87]. There was a significant increase in the whole blood cadmium levels during late pregnancy, in particular [80,88,89]. This increase in cadmium levels may be related to enhanced cadmium absorption due to an upregulated iron absorption, particularly during the late pregnancy period [43,80], because mechanisms of iron absorption are similar to those of other divalent metals, particularly manganese and cadmium [4,5]. However, blood cadmium concentrations have rarely been reported to decrease after menopause. Blood cadmium levels were found to be higher in menopausal than in premenopausal women, and higher in postmenopausal women than in men of corresponding age. By contrast, one study found no statistically significant differences in blood cadmium levels in postmenopausal and premenopausal women [90]; however, urinary cadmium concentrations were higher in women than in men aged over 50 years [87], with between-gender differences greater in individuals aged >50 years than those aged <50 years [91]. In addition, cadmium levels were significantly higher in the hair of elderly females than males [92]. Similarly, our recent study [93] found that blood cadmium concentrations were higher in women than in men aged >50 years, and there was no association between iron deficiency and elevated cadmium levels in postmenopausal women [94,95] or in men [85,96]. Thus, sex-specific differences in cadmium levels at older ages are not only due to iron–cadmium interaction, but also due to a higher absorption rate in females than in males that could be also influenced by other confounding factors (iron stores; Table 3)

Table 3
Behavior of blood/urine cadmium concentrations according to age- and sex-related variables

Variables	Refs (*n*)	Study populations and findings
Age	[74] (5,924)	Korean general population aged ≥20 y; KNHANES 2008–2010/GM of blood cadmium had a significant increase with age
	[53] (8,793)	U.S. general population NHANES 2009–2010/GM of urinary cadmium had a significant increase with age
	[86] (2,257)	U.S. general population aged ≥6 y; NHANES 2003–2004/GM of urinary cadmium had a significant increase with age
	[87] (1,055)	Bangladesh general population aged ≥8 y/median urinary cadmium levels had a significant increase with age
Sex	[53] (8,793)	U.S. general population; NHANES 2009–2010/GM of blood cadmium in men vs. women: 0.279 μg/L vs. 0.326 μg/L*
	[74] (5,924)	Korean general population aged ≥20 y; KNHANES 2008–2010/GM of blood cadmium in men vs. women: 0.780 μg/L vs. 1.194 μg/L*
	[86] (2,257)	U.S. general population aged ≥6 y; NHANES 2003–2004/GM of urinary cadmium in men aged ≥12 y was lower than in women; but no difference in children aged 6–11 y
	[87] (1,055)	Bangladesh general population aged ≥8 y/median urinary cadmium level in men aged 30–50 y, 51–88 y vs. women; 0.66 μg/L vs. 0.81 μg/L, 0.88 μg/L vs. 1.1 μg/L
Menopause	[93] (3,700)	Korean general population/blood GM of cadmium in premenopausal vs. postmenopausal women: 0.995 μg/L vs. 1.165 μg/L*
	[87] (149)	Bangladesh general population aged >51 y/median urinary cadmium in women vs. men: 1.1 μg/L vs. 0.88 μg/L
	[91] (1,670)	German general population aged ≥25 y/between-gender differences in blood GM of cadmium greater in individuals aged >50 y than aged <50 y
Pregnancy	[97] (120)	Spanish general population/no significant changes in urinary GM of cadmium during pregnancy and postpartum: 0.44 μg/L vs. 0.64 μg/L
	[88] (2,882)	Chinese general population/significant changes in the blood median cadmium between during late pregnancy periods and nonpregnant women; 0.75 μg/L vs. 0.5 μg/L
	[89] (281)	Bangladesh general population/median blood cadmium increased 15% from early pregnancy (0.5 μg/L) to 6 mo postpartum
	[80] (216)	Swedish general population/median blood cadmium increased 13% from early pregnancy (0.16 μg/L) to 3 mo postpartum

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

[53,74,80,86–89,91,93,97,98]. Further study is required to clarify the source of these differences. However, age-related increase in blood cadmium is remarkable because of increase in oral exposure with age [53,74,86].

5. Summary

Exposure is the major determinant of blood/urine metal concentrations in humans. This review focused on the general population without occupational exposure. We assumed a similar exposure between the two sexes, which is a limitation of this review, and discussed the kinetics of the toxic metals with a similar metal–iron interaction, such as manganese, lead, and cadmium, in relation to menstrual, reproductive, and menopausal factors.

The potential causes of sex-specific differences in the blood levels of manganese, lead, and cadmium differ from each other, although all three are associated with iron deficiency. Therefore, other factors such as estrogen effects, or absorption rate as well as iron deficiency, should be considered when addressing environmental exposure to toxic metals and sex-specific differences in the blood levels of these metals.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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