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Review Article

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

Byung-Kook Lee [1], Yangho Kim [2,*]

[1] Korean Industrial Health Association, Seoul, Korea
[2] Department of Occupational and Environmental Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

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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

* Corresponding author. Department of Occupational and Environmental Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, 290-3 Cheonha-Dong, Dong-Gu, Ulsan 682-060, Korea.
E-mail address: yanghokm@nuri.net (Y. Kim).

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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.