Chapter 3

Effect of Iron Deficiency on the Increased Blood Divalent Metal Concentrations

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.78958

Abstract

The apical divalent metal transporter 1 (DMT1) and the iron exporter ferroportin 1 (FPN1) are responsible for the absorption of iron and other divalent metals (manganese, lead, and cadmium). Thus, an iron-deficient diet can lead to excess absorption of manganese, lead, and cadmium, and high blood concentrations of these metals. Relative to males, females of childbearing age have higher blood concentrations of manganese because of their lower blood concentrations of ferritin. Moreover, relative to premenopausal women, menopausal women have lower blood manganese levels because their higher concentrations of ferritin. There is also a significant increase in the whole blood manganese level throughout pregnancy due to the upregulation of iron absorption at this time. Several previous studies reported a temporal relationship between iron deficiency and increased blood lead concentrations in children. However, this association does not occur in postmenarcheal or postmenopausal women because estrogen promotes bone mineralization and redistributes blood lead into the bone, overshadowing the effect of ferritin on blood lead level. Although blood cadmium concentrations are higher in females of childbearing age because of their lower ferritin concentrations, there is no association of blood cadmium and iron levels in infants and postmenopausal women.

Keywords: manganese, lead, cadmium, iron deficiency, divalent metal transporter 1, ferroportin

1. Introduction

Iron deficiency affects approximately one-third of the world's population, and is the most common nutritional deficiency [1]. Iron deficiency is most common in rapidly growing children (aged 6 months

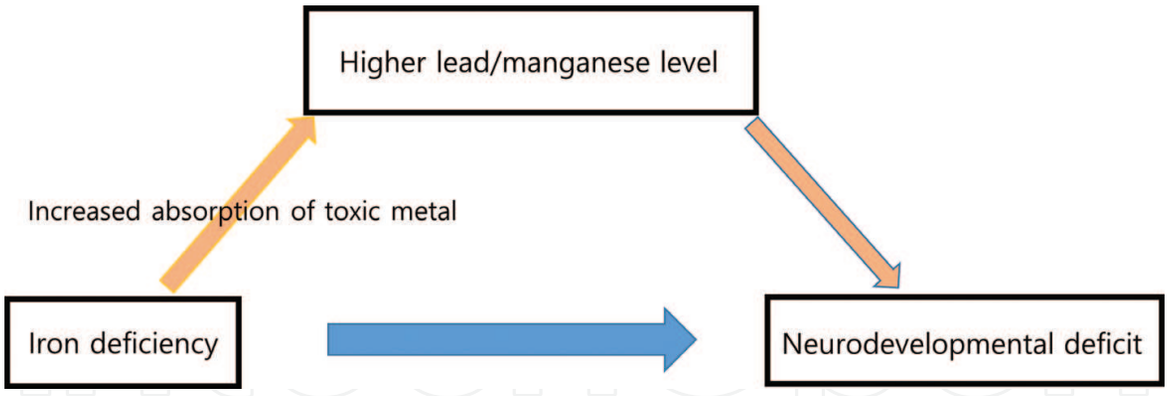

Figure 1. The direct and indirect effect of iron deficiency on neurodevelopment in children.

to 3 years) who have inadequate intake of dietary iron [2]. Iron deficiency is the only micronutrient deficiency that also has a high prevalence in virtually all developed countries [3].

Toxic metals, such as manganese, lead, and cadmium, have become ubiquitous in the developed world, and general populations are increasingly exposed to these metals. Inhalation of toxic metals is the most common route of exposure in environmental and occupational settings [4]; food intake is the major source of exposure in general populations and in children, who are more vulnerable to toxic metals absorbed through the intestine [5]. The mechanisms of iron absorption are similar to those of other divalent metals [6–11], and an iron-deficient diet can lead to excess absorption of manganese [12–14], lead [15–17], and cadmium [18–20].

The gastrointestinal absorption of these divalent metals appears to be mediated by intestinal iron transporters, such as apical divalent metal transporter 1 (DMT1), which also mediates the uptake of other divalent metals [21]. There is up-regulation of DMT1 in the presence of low iron stores [22], and this explains the increased uptake of divalent metals [13, 14] and the higher blood concentrations of these metals in iron-deficient individuals. New evidence indicates that the iron exporter ferroportin 1 (FPN1) also transports these divalent metal ions [8–11]. Thus, the major transporters responsible for the absorption of nonheme iron, apical DMT1 and the FPN1, also function in the absorption of divalent toxic metal ions.

Elevated levels of manganese, lead, and cadmium may adversely affect neurodevelopment, cognitive and motor development, and behavioral development in children [23]. Iron deficiency in children may lead to cognitive impairment, caused by the deficiency of iron itself or by the increased levels of these toxic metals (**Figure 1**). Therefore, decreased levels of iron, combined with increased levels of cadmium, manganese, or lead, have major effects on the neurodevelopment of children [24].

2. Effect of iron deficiency on blood concentrations of manganese, lead, and cadmium

2.1. Manganese

Manganese is a naturally occurring element that is abundant in the environment. It is also an essential dietary nutrient, and the body requires specific concentrations for proper function.

More specifically, at the physiological level, manganese functions in bone formation, protein and energy metabolism, and metabolic regulation; at the molecular level, it functions as a cofactor for a number of enzymes [25]. Because manganese is an essential element, homeostatic mechanisms regulate its absorption, disposition, and biliary excretion [25]. These homeostatic processes also play important roles in manganese toxicokinetics, which differ from those of nonessential toxic metals, such as lead and cadmium. Inhalation is the most common route of adult manganese exposure in environmental and occupational settings [25], whereas food is the major source of absorbed manganese in children, who are more vulnerable than adults to manganese due to higher intestinal absorption rate. Another source is the presence of a portal systemic shunt due to liver cirrhosis, which impairs the clearance of manganese through biliary excretion [25]. Blood manganese concentration appears to be related to manganese body burden on a group basis [25]. Chronic occupational exposure to manganese can cause a neurologic impairment known as "manganism," a motor disorder with some similarities to idiopathic Parkinson's disease in adults [25]. Recently, manganese excess have been reported to be associated with neurodevelopmental deficits, reduced IQ, and increased risk of behavioral problems, and attention deficit hyperactivity disorder in children [26].

Animal and human studies have demonstrated that iron deficiency markedly enhances intestinal absorption of manganese [12, 13]. DMT1 and FPN1 are responsible for the absorption of iron and other essential divalent metals, particularly manganese. Thus, an iron-deficient diet can lead to excess absorption of manganese; therefore, iron deficiency can be a risk factor for the accumulation of toxic levels of manganese in the central nervous system [27].

Previous studies have shown that iron deficiency leads to increased blood manganese concentrations in adults and children [14, 28, 29]. We recently showed that blood manganese levels are also elevated in iron-deficient infants [30]. After iron therapy, the blood manganese levels of iron-deficient infants declined significantly relative to their pretherapy levels (2.045 vs. 2.971 μg/dL), and their hemoglobin and ferritin levels increased significantly. Females of childbearing age have reduced concentrations of ferritin, and therefore increased levels of blood manganese relative to males [14, 31–33] and relative to menopausal women (who have higher levels of ferritin) [33] (**Figure 2**). Previous research reported significant increases in the whole blood manganese levels throughout pregnancy [34–38] (**Table 1**). This may be related to the enhanced absorption of manganese due to upregulation of iron absorption, particularly during the late periods of pregnancy [39], because the mechanisms of iron and manganese absorption are similar.

2.2. Lead

Lead is a widespread environmental pollutant that can damage the central nervous, peripheral nervous, renal, cardiovascular, reproductive, and hematological systems in adults [40]. Exposure to lead induces a wide range of adverse health effects in children [40], because children are more sensitive to toxic effects. Very low blood lead levels (<10 μg/dL) have been associated with reduced IQ, deficits in executive function, and attention deficit hyperactivity disorder in children [26]. The environmental exposure to lead are mainly from leaded gasoline, lead paint such as lead paint-contaminated dust and soil, water from lead pipes, and emissions due to industrial activities [40]. Thus, main route of environmental exposure to lead is inhalation or ingestion [40]. Bone lead reflects total body burden of lead. However, blood lead concentration accounts for a part of the total body burden, and it reflects a recent exposure [40].

Figure 2. Changes in blood manganese levels according to sex, age, and menstrual status.

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* [14]
	(n = 297)	Canadian general population/GM of blood Mn in female vs. male: 0.750 vs. 0.675 μg/dL* [31]
	(n = 7720)	USA general population (NHANES 2010–2011)/GM of blood Mn in female vs. male: 0.99 vs. 0.87 μg/dL* [32]
Menopause	(n = 1826)	Korean general population KNHANES 2008–2009/GM of blood Mn in premenopause vs. postmenopause: 1.443 vs. 1.296 μg/dL* [33]
	(n = 66)	Sweden general population/Maternal blood median Mn during pregnancy at 3rd, vs. 2nd, vs. 1st trimester 1.26 vs. 1.04 vs. 0.85 μg/dL [34]
Pregnancy	(n = 34)	Australian general population/Maternal blood Mn during pregnancy from 10 to 20 weeks vs. 25 vs. 34 weeks; 0.82 vs. 0.94 vs. 1.26 μg/dL [35]
	(n = 290)	Canadian general population/Maternal blood GM Mn during pregnancy at 3rd, vs. 2nd, vs. 1st trimester vs. nonpregnant 1.56 vs. 0.95 vs. 0.85 and 0.746 μg/dL [36]
	(n = 470)	Canadian general population/Maternal blood AM Mn during pregnancy at delivery vs. nonpregnant; 2.4 vs. (0.8–1.2) μg/dL [37]
	(n = 1085)	USA general population/blood GM Mn in pregnancy vs. nonpregnant; 1.19 vs. 1.02 μg/dL [32]
	(n = 265)	Korean general population/blood GM Mn in pregnancy; 2.25 μg/dL [38]

AM, arithmetic mean; GM, geometric mean; KNHANES, Korea National Health and Nutrition Examination Survey; NHANES, National Health and Nutrition Examination Survey [22].

*Statistically significant.

Table 1. Behavior of blood manganese (Mn) concentrations according to gender-related variables.

Many cross-sectional studies have found that iron-deficiency anemia in children is associated with poor cognitive development, poor motor development, and behavioral problems due to the increased uptake of lead [23, 24]. There is also evidence that decreased cognitive development of children with iron deficiency persists after iron treatment and correction of anemia [23, 24]. Approximately 90% of the lead in the body is stored in the skeleton [40], and lead in bones has a half-life ranging from years (trabecular bone) to decades (cortical bone).

Several previous studies have assessed the temporal relationship between iron deficiency and increased blood lead concentration [15, 16, 41]. A longitudinal study showed an association between iron deficiency and high blood lead level in young children who had blood lead

levels ranging from less than 5 to 40 μg/dL [42]. Another study of children aged 10–15 years reported the mean blood lead concentration was 6.9 μg/dL in iron-deficient children and 4.3 μg/dL in those with normal iron levels, and that iron supplementation significantly decreased blood lead concentrations in the former group [16]. A clinical trial assessing the impact of iron supplementation on blood lead concentrations in infants with iron deficiency found that blood lead concentration decreased as iron status improved [15, 41]. In contrast to these studies, other studies have found no association between iron deficiency and increased blood lead concentration [42–46].

This discrepancy may be partly due to the different ages of the study subjects and the extent of their exposures to lead. For example, studies of older female children or adolescents reported no association of blood iron and lead levels [42, 44, 47]. Postmenarcheal women have lower blood lead concentrations than men, because estrogen promotes bone mineralization and redistributes blood lead into bone, and this estrogen effect overshadows the increasing effect of ferritin on blood lead level [48]. Hence, there is no association between high blood lead level and iron deficiency in postmenarcheal adolescents [48]. Some studies of children with lower blood lead concentrations (11.0 and 11.4 μg/dL) reported no association of blood lead and iron levels [43, 45]. However, longitudinal studies of children with blood lead levels in a similar age range reported an association between iron status and blood lead concentration following iron supplementation [16, 41]. Furthermore, we recently showed that blood lead levels are elevated among iron-deficient infants with very low blood lead concentrations (1.416–1.846 μg/dL) [15]; moreover, iron therapy significantly decreased the blood lead levels of iron deficient infants [12]. Even minor increases in blood lead concentration due to iron deficiency may have clinical implications in children, considering the lack of evidence that any level of lead in the blood can be considered safe [26].

2.3. Cadmium

Cadmium is a ubiquitous environmental pollutant, and the main environmental sources are air, soil, and water contamination due to industrial activities, use of phosphate fertilizers, combustion of motor fuels, and particles released by tire wear. Smoking is the most important source, because tobacco plants, like other plants, take up cadmium from soil. In nonsmokers, diet is the major source of cadmium exposure [49]. Cadmium increases the risk of overall mortality and cardiovascular including hypertension, neurologic, renal, and developmental diseases in adults [49]. A recent paper showed that prenatal low-level exposure to cadmium had adverse effects on neurodevelopment in children [50]. Cadmium levels in the body increase with age, because only small amounts (0.01–0.02%) are excreted each day [49]. Blood cadmium is a biomarker of recent exposure, and urinary cadmium is a biomarker of lifetime exposure [49].

The body absorbs iron and cadmium by similar mechanisms [6, 22], and animal experiments have shown there may be metabolic interactions between cadmium and iron [6, 22]. In particular, animals with low iron stores have increased cadmium uptake [18, 20, 51]. Moreover, high cadmium concentrations are present in premenopausal women with low iron stores [33, 42, 52–55]. Females of childbearing age have higher blood cadmium concentrations than males because of their lower ferritin levels [53, 56–61]. There is also a significant increase

in the whole blood cadmium level during late pregnancy in particular [53, 62–64] (**Table 2**). This increase may be caused by an enhanced cadmium absorption due to upregulated iron absorption during late pregnancy [53], because the mechanisms of iron absorption are similar to those of other divalent metals, particularly manganese and cadmium [6, 7]. However, there is no association between iron deficiency and elevated cadmium levels in postmenopausal women [60, 65, 66]. This may be because of the higher cadmium absorption rate in older-aged females than males, and the interaction of iron and cadmium uptake. Our recent study showed no association between iron deficiency and cadmium concentration in infants [67], but assessment of the same study subjects showed that iron deficiency was associated with increased blood lead and manganese concentrations [15, 30]. It is possible that the lower likelihood of exposure to cadmium in infants explains the lack of an association of blood cadmium level with iron deficiency in these individuals. The placenta may partially prevent

Variables	No. (n)	Study subjects and findings
Gender	(n = 7920)	US general population NHANES 2011–2012/
		GM blood cadmium in men vs. women: 0.255 vs. 0.304 μg/L* [57]
	(n = 5924)	Korean general population aged 20 years or more; KNHANES 2008–2010/GM blood cadmium in men vs. women: 0.780 vs. 1.194 μg/L* [56]
	(n = 2257)	US general population aged 6 years and older; NHANES 2003–2004 /
		GM urinary cadmium in men aged 12 years or older lower than women; but no difference in children aged 6–11 [58]
	(n = 1055)	Bangladesh general population aged 8 years and older/Median urinary cadmium in men aged 30–50, 51–88 years vs. women; 0.66 vs. 0.81, 0.88 vs. 1.1 μg/L [59]
Menopause	(n = 3700)	Korean general population/
		blood GM cadmium in premenopause vs. postmenopause: 0.995 vs. 1.165 μg/L* [60]
	(n = 149)	Bangladesh general population aged more than 51 years/median urinary cadmium in women vs. men; 1.1 vs. 0.88 μg/L [59]
	(n = 1670)	German general population aged 25 or older/between-gender differences in blood GM cadmium greater in subjects >50 than <50 years of age [61]
Pregnancy	(n = 120)	Spain general population/No significant changes in urinary GM cadmium during pregnancy and postpartum; 0.44 vs. 0.64 μg/L [62]
	(n = 2882)	Chinese general population/Significant changes in the blood median cadmium between during late pregnancy and nonpregnancy; 0.75 vs. 0.5 μg/L [63]
	(n = 281)	Bangladesh general population/Median blood cadmium increased 15% from early pregnancy (0.5 μg/L) to 6 months postpartum [64]
	(n = 216)	Swedish general population/Median blood cadmium increased 13% from early pregnancy (0.16 μg/L) to 3 months postpartum [53]

GM, geometric mean; KNHANES, Korea National Health and Nutrition Examination Survey; NHANES, National Health and Nutrition Examination Survey [22].

*Statistically significant.

Table 2. Behavior of blood/urine cadmium concentrations according gender-related variables.

fetal exposure to cadmium [68] and only 5–10% of maternal blood cadmium is transferred to human milk, because metallothionein binds to cadmium in blood cells [69]. Moreover, blood cadmium concentrations tend to increase with age [49, 70–72].

3. Toxicological implications

The effect of iron deficiency on blood concentrations of other divalent metals has several clinical and toxicological implications. First, the present paper emphasizes the importance of assessing the iron level and hematologic status of individuals for studies of environmental exposure to divalent metals (manganese, lead, and cadmium) in general populations. In particular, given the high prevalence of iron deficiency in children, iron deficiency status must be considered as an important factor affecting their susceptibility to heavy metal toxicity, especially for environmental health risk assessments of low exposure to these toxic metals. Second, our results also emphasize that exposure to neurotoxic metals may aggravate iron-related developmental and behavioral problems in children and lead to subclinical neuropsychological problems in adults.

4. Conclusions

The apical divalent metal transporter 1 (DMT1) and the iron exporter ferroportin 1 (FPN1) are responsible for the absorption of iron and other divalent metals (manganese, lead, and cadmium). Thus, an iron-deficient diet can lead to excess absorption of manganese, lead, and cadmium, and high blood concentrations of these metals. Relative to males and postmenopausal women, females of childbearing age have higher blood concentrations of manganese because of their lower blood concentrations of ferritin. Several previous studies reported a temporal relationship between iron deficiency and increased blood lead concentrations in children. Blood cadmium concentrations are higher in females of childbearing age because of their lower ferritin concentrations than in men.

Conflict of interest

The author declares no conflicts of interest.

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