

Effects of Cadmium Intake on Bone Metabolism of Mothers during Pregnancy and Lactation

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OHTA, H., ICHIKAWA, M. and SEKI, Y. *Effects of Cadmium Intake on Bone Metabolism of Mothers during Pregnancy and Lactation.* Tohoku J. Exp. Med., 2002, **196**(1), 33–42 — Cadmium (Cd) is a heavy metal that exists ubiquitously in the environment, and it interacts with essential elements such as zinc, copper, iron, and calcium (Ca). Particularly, Cd interferes with Ca and vitamin D metabolism in bone kidney and intestine. The interaction between Cd and Ca in bone, intestine, and kidney may result in the disorder of bone metabolism. On the other hand, pregnancy and lactation are also important physiological factors affecting bone metabolism in the mother. Ca absorption is decreased by competition with Cd in the intestine, and more Ca is released from maternal bone and transferred to neonate by lactation. In the intestine, Cd uptake competes with Ca uptake. Cd causes a marked decrease in bone density compared to the normal decrease in bone mineral density during lactation. Lactation is an important factor contributing to the decrease in bone mineral density and Cd has an additive effect of decreasing bone metabolism of mother animal, although the Cd intake level is relatively low (approximately 3–14 $\mu\text{gCd/kg/day}$). The relationship among maternal Cd intake, renal function and bone metabolism and the interaction between Cd and Ca during lactation are reviewed herein, together with additional data obtained recently in our laboratory. — bone mineral density; cadmium uptake; calcium metabolism; lactation pregnancy; renal function
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Cadmium (Cd) is a ubiquitous heavy metal that is mainly taken in by the body through the diet, in the absence of such adverse habits as smoking, and environmental exposure. Cd is a toxic metal that accumulates selectively the liver and in the kidney. Cd is detoxified and stored mainly in the two organs as metallothionein-bound Cd (Cd-MT). The dynamic equilibrium of Cd-Mt is maintained. Essential elements, such as calcium (Ca), iron, zinc, copper, vitamin D, and the chemical form of Cd influence intestinal absorption and/or toxicity of Cd in humans and animals (Foulkes 1985; Nordberg et al. 1985; Kjellström 1986, 1992; Groten et al. 1991, 1992; Goyer 1997). Renal dysfunction and bone metabolism disorder are known to be the representative adverse health effects of chronic Cd toxicity in humans and animals. Other effects of Cd exposure on humans and animals are also recognized as follows: cases of acute and chronic toxicity due to occupational and environmental exposure, such as anemia, respiratory disorder, hypertensive and cardiovascular effects, nervous system symptoms, cancer of the lung and prostate, toxic effects on the placenta and teratogenicity (Kjellström 1992; WHO 1992; Friberg et al. 1986; Cherian and Goyer 1989).

Itai-itai disease is known to be an adverse health effect of chronic Cd toxicity in Cd-polluted areas in Japan. It is characterized by multiple fractures and distortion of leg bones which cause severe pain in the affected person. The disease exhibits a mixed pattern of osteomalacia and osteoporosis in combination with kidney damage (Friberg et al. 1986; Tsuchiya 1978; Kjellström 1986). Although the mechanisms of the toxic effects of Cd on bone metabolism are not well known, it is surmised that Cd may disrupt Ca metabolism. It is not clear whether these effects of Cd on Ca metabolism are secondary to renal dysfunction, or whether there is a direct effect on the Ca pathways in kidney and intestine. (Tsuchiya 1978; Goering et al. 1995; Kjellström 1992).

Metallothionein and Cd uptake from gastrointestinal tract, and distribution and toxicity of Cd

The rate of Cd absorption from the gastrointestinal tract is low; in humans, the uptake is estimated at 5% with a variation of 3–7%, and in experimental animals, it is less than 2% and depends on the composition of the diet, including Ca intake (Nordberg et al. 1985; Foulkes 1986; Goering et al. 1995; Brzoska and Moniuzsko-Jakoniuk 1998; Ohta et al. 2000).

Ca is absorbed in the gastrointestinal tract by both active and passive mechanisms. Active intestinal transport occurs mainly in the duodenum and is regulated by 1, 25-dihydroxyvitamin D, partly through its stimulation of calbindin 9 kDa. Passive transport of Ca appears to be an unregulated, nonsaturable process that occurs throughout the small intestine; the rate of passive transfer of Ca into intestinal cells is directly proportional to the intraluminal concentration of Ca (Bringhurst 1995; Halbert and Tsang 1992).

Hamilton and Smith (1978) showed that a Ca-deficient diet influences the distribution of Cd in organs and observed an increased Cd retention in the small intestine and kidneys. It has been found that after perfusion of the intestine in situ, a large dose of Ca may inhibit Cd absorption (Foulkes 1986). It has also been reported that a Ca-deficient diet increases Cd accumulation in the liver and kidneys in comparison to animals exposed to the same Cd exposure level but given normal Ca diet (Larsson and Piscator 1971; Washko and Cousins 1977).

Cd suppresses the absorption of Ca directly by competing with Ca^{2+} ions for binding sites in the epithelium of intestinal villi and indirectly by disturbing vitamin D metabolism in kidney (Bredderman and Wasserman 1974; Washko and Cousins 1977; Foulkes 1986; Felley-Bosco and Diezi 1992).

Cd-MT is a low molecular weight metal-binding protein. When Cd-MT is administered

parenterally to mice and rats, exogenous Cd-MT is much more toxic to kidney than Cd ion. On the other hand, intracellular Cd-MT exerts a protective effect against Cd toxicity at low levels of Cd exposure. External Cd-MT is toxic to the kidney; it is released by the liver into serum (Waalkes and Perez-Olle 2000). In the case of oral Cd administration, Cd-MT can be taken up in its intact form by intestinal cells and transported selectively to the kidney. On the other hand, much more Cd ions are transferred into the liver and accumulated in the form of Cd-MT (Cherian and Goyer 1987; Ohta and Cherian 1991)

Chan and Cherian (1993) reported that pregnancy can mobilize hepatic Cd-MT, which can be transferred to the kidney and placenta through the plasma in Cd-pre-treated rats. Although intestinal Cd uptake is not affected by the intracellular MT, MT seems to have a major limiting effect on the rate and extent of release of Cd from the intesine and the subsequent distribution and deposition in the tissues (Min et al. 1991, 1992). Ohta and Cherian (1991) also reported that the intestinal Cd bound by MT can reduce the rate of Cd release from the intestinal cells and its subsequent transfer to the liver. When the oral dose of Cd is low, Cd leaving the intestine changes its chemical form into Cd-MT in the intestine; that is, intracellular Cd is bound by MT in the intestine, released into blood across the basolateral membrane, and transported selectively to kidney and accumulated (Bhattacharyya et al. 2000; Ohta and Cherian 1991; Min et al. 1991, 1992). Dorian et al. (1992, 1995) speculated that this pathway may explain the reason why renal dysfunction, rather than hepatic dysfunction, predominates in the case of continuous dietary Cd ingestion (Waalkes and Perez-Olle 2000).

The chemical form of Cd is modified by MT in the intestinal tissue. Particularly, at a low dose of Cd, Cd competes with Ca and disturbs Ca absorption in the intestine. Much more Cd in the form of Cd-MT is transported to

the kidney rather than the liver. As a result, Cd is absorbed and accumulated in the kidney, although the mechanism of Cd absorption in the kidney is still unclear.

Cadmium effects on renal dysfunction and Ca metabolism disorder

Under physiological conditions, Ca concentration in the serum is kept within a narrow range due to precise hormonal regulation in which parathyroid hormone, calcitonin and $1, 25\text{-(OH)}_2\text{D}_3$ take part by acting directly on their target organs: intestine, bone and kidney. In the case of reduced Ca concentration in the serum (for example, in conditions of low dietary Ca consumption), Ca is mobilized from the bone, which is the main storage site of Ca in the organism (Bronner and Stein 1995; Brzoska and Moniuszko-Jakoniuk 1998).

The kidney, which plays an important role in maintaining Ca homeostasis, is a target organ for Cd toxicity under conditions of chronic Cd exposure (Friberg et al. 1986; Bronner and Stein 1995; Kjellström 1986, 1992; WHO 1992). Because renal damage results from chronic Cd exposure, a Cd-related inhibition of the renal conversion of 25(OH)-vitamin D to $1\alpha 25\text{(OH)}_2\text{-vitamin D}$ may lead to decreased Ca reabsorption, demineralization of bone, and eventually osteomalacia (Friberg et al. 1986; Kjellström 1986; Nogawa et al. 1987).

The disturbance of vitamin D metabolism in the kidney leads to a decrease in synthesis of the low molecular weight Ca binding protein (CaBP), and thereby to decreasing Ca absorption in enterocytes of the intestine. Decreasing dietary Ca intake leads to enhanced parathyroid hormone (PTH) secretion, which, in turn, stimulates renal 1α -hydroxylase $25\text{-hydroxy-cholecalciferol}$ production. This enzyme is responsible for the conversion of $25\text{-hydroxy-cholecalciferol}$ to $1, 25\text{-dihydroxycholecalciferol}$ ($1, 25\text{-[OH]}_2\text{D}_3$) in the mitochondria of renal tubular cells. In rats fed a low-Ca diet, an increase in the conversion of 25(OH)D_3 to $1, 25\text{-$

(OH)₂D₃ in the kidney has been observed (Boyle et al. 1971; Brzoska and Moniuszko-Jakoniuk 1998). Lorentzon and Larsson (1977) showed that adult rats exposed to Cd during normal Ca intake exhibited a decrease in the conversion of 25(OH)D₃ to 1, 25-(OH)₂D₃ in kidney mitochondria, while low-Ca diet caused an increase of 1, 25-(OH)₂D₃ synthesis and abolished the inhibiting action of Cd.

On the other hand, Suda et al. (1974, 1990) showed that Cd-MT did not significantly influence 1 α -hydroxylation of 25(OH)D₃ in the kidney, while free Cd²⁺ ions were effective in this regard. These results suggest that the induction of MT in the kidney protects the action of 1 α -hydroxylase 25(OH)D₃. Kimura et al. (1974) also reported that in rats fed both a low-Ca and low-vitamin D diet with Cd exposure for three weeks, a slight decrease of 1 α -hydroxylase 25(OH)D₃ activity was observed after Cd exposure at 10 and 30 ppm, and at 300 ppm of Cd, the enzyme activity decreased to 50%.

Kawamura et al. (1978) reported that Ca deficiency leads to enhanced Cd accumulation and intensifies the toxic effect of Cd in bones. They also found that Cd in drinking water did not influence Ca content in the femoral bone of rats fed a diet with 0.5% Ca; in contrast, in the case of a low-Ca diet (0.001% Ca), Cd-induced histopathological changes in bones, resembling osteomalacia, were evident. Itokawa et al. (1974) also observed histopathological changes in the cortical tissue of the femoral bone, manifested by a significant decrease in the number of osteocytes in cortical bone tissue, in rats given Cd during low-Ca intake.

Other studies also showed that the reduced Ca intake intensifies the influence of Cd on bone tissue (Larsson and Piscator 1971; Wang et al. 1994; Whelton et al. 1994). As a consequence, the resorption of Ca from bones for compensation of calcaemia increases. As a result of Cd-induced renal tubular injury, excessive amounts of Ca and Cd are lost via the urine, leading to further decrease of Ca content in the

bones (Felley-Bosco and Diezi 1992; Brzoska and Moniuszko-Jakoniuk 1998).

From these studies, it is suggested that the mechanism of indirect Cd action on bone tissue is reflected by the disturbance of intestinal Ca absorption and excessive urinary loss of Ca due to Cd-induced renal tubular damage.

Cd is taken up in the bone. Oral Cd administration can induce a burst of bone resorption. Moreover, the daily consumption of drinking water with low Cd concentration (15 ug/liter) causes a transient increase in ⁴⁵Ca released from bone over a period of two to three weeks (Sacco-Gibson et al. 1992; Wilson and Battacharyya 1997). From these data, the authors suggest that Cd interacts with the bone to cause an up-regulation of the resorptive processes that occur during the normal dynamic cycle of bone remodeling. Ogoshi et al. (1992) reported that Cd accumulates in the bone during growth and remodeling, making the bone highly susceptible to defects in mechanical properties. They also showed a correlation between Cd in bones and bone strength decrease, suggesting that Cd directly affects the mechanical properties of the bone.

Most studies have indicated that Cd may have a direct effect on bone mineralization, possibly related to Ca deficiency, and an indirect effect on Ca absorption in the intestine through vitamin D hydroxylation in the kidney, which may lead to osteoporosis and/or osteomalacia (Kjellström 1986; WHO 1992; Berglund et al. 2000).

Recently, Ohta et al. (2000) reported that the effects of Cd on renal dysfunction and bone metabolism disorder may be changed depending on the conditions (the duration and the dose) of oral Cd administration, and the critical concentration of Cd in the kidney, reflected by the enzymeuria and the biochemical indexes of bone metabolism, may also be changed. It has also been reported that exposure to low levels of Cd is associated with an increased risk of osteoporosis (Jarup 1998; Alfven et al. 2000).

Cadmium effects on bone metabolism during lactation

Female animals are susceptible to Cd-induced bone loss, increased bone resorption, and loss of bone Ca. To compensate for the increased Ca requirement during lactation, it is thought that maternal adaptation takes place, including increased intestinal Ca absorption, renal conservation of Ca, and increased resorption of Ca from the bone. Bone turnover is increased during lactation in rats, as indicated by changes in histomorphometric parameters of bone during lactation (Miller et al. 1989; Fukuda and Iida 1993; Kovacs and Kronenberg 1997). The lactational decrease in bone density may not adversely affect the bone in the long term, although occasionally the normal lactation-induced decrease in bone density may be excessive, leading to fractures and a clinical diagnosis of osteoporosis. The bone density loss during of lactation is substantially reversed during weaning, such that the maternal bone is able to meet the Ca requirements of lactation with few, if any, long-term consequences (Sowers et al. 1993). The reversibility of bone density loss has also been found in the lactating rat model (Kovacs and Kronenberg 1997).

Since Cd-induced bone lesion or defects may be mediated by renal tubular dysfunction and are thought to be a secondary effect of renal dysfunction, other effects, direct or indirect, are also suggested (Kjellström 1986; Roels et al. 1993; Wang and Bhattacharyya 1993). When Ca absorption in the intestine and kidney is inhibited by Cd, Ca metabolism related to bone remodeling may be affected, consequently causing bone mineral density decrease and adversely affecting on bone strength (Bredderman and Wasserman 1974; Washko and Cousins 1977; Foulkes 1986; Goyer et al. 1994; Newitt 1994; Bronner and Stein 1995; Brzoska and Moniuszko-Jakoniuk 1998).

Ohta et al. (2001) reported that in mother rats subject to oral Cd administration, a signifi-

cant decrease of femoral bone mineral density was found depending on the oral dose of Cd during pregnancy and lactation, compared with that in control mother rats (Fig. 1). Particularly, Cd exposure during lactation caused a marked dose-dependent decrease in femoral bone mineral density of mother rats. Markers of bone resorption (deoxypyridinoline/creatinine, hydroxyproline/creatinine) are elevated significantly, but not osteocalcin in plasma for bone formation. On the other hand, the levels of B2-MG, amino acid, and NAG reflecting renal dysfunction are elevated in mother rats given Cd at 2 and 5 mgCd/kg six days a week for 10 weeks (about 7 and 14 $\mu\text{gCd/kg}$, based on estimation at the intestinal absorption rate of 0.5%) during pregnancy and lactation (Ohta et al. 2001, unpublished data).

Under normal physiological conditions, the remarkable decrease of bone mineral density due to Cd exposure during pregnancy and lactation, particularly during lactation, is interesting in terms of evaluating the effect of low-Cd intake on bone metabolism.

Experiments have shown that dietary Cd increased bone mineral loss to a significantly greater extent in ovariectomized animals than in controls (Bhattacharyya et al. 1988). Dietary Cd exposure had a more pronounced effect on the bone of pregnant or lactating mice than on that of non-pregnant controls. Cd increased bone resorption in ovariectomized and sham-operated dogs without renal dysfunction or calciotropic hormone interaction (Bhattacharyya et al. 1988, 1992; Sacco-Gibson et al. 1992). However, in our study, the decrease of bone density in mother rat was found under normal physiological conditions in the absence of ovariectomization and dietary control of Ca. In mother rats given Cd orally with normal Ca diet, it was found that the uptake of Cd and the degree of Cd accumulation in the kidney were higher than those in the liver (Ohta et al. unpublished data).

Based on the above results, the mechanism

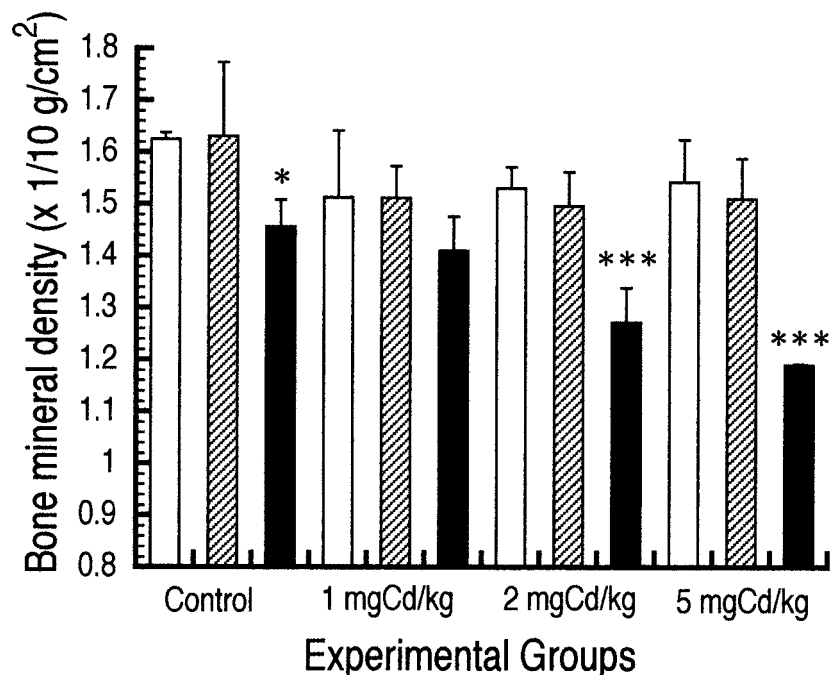


Fig. 1. Bone mineral density in femur of mother rats after oral Cd administration during pregnancy and lactation.

*Significant differently compared to the non-pregnant rats of each group at $p < 0.05$ by ANOVA-PLSD test.

**Significantly differently compared to the pregnant rats of control group at $p < 0.05$ by ANOVA-PLSD test.

Experimental groups:

□, non-pregnant; ▨, pregnant and non-lactating; ■, pregnant and lactating.

underlying the decrease in the bone mineral density of mother rat that ingested Cd during pregnancy and lactation is speculated and shown in Fig. 2. Cd hinders Ca uptake in intestinal tract, and Cd accumulated in the kidney causes renal dysfunction and disorder of vitamin D metabolism. On the other hand, in mother rat, Ca mobilization from the bone is promoted to supply Ca to the fetus and neonate through the placenta and breast milk, although intestinal Ca absorption is hampered by competition with Cd and urinary excretion of Ca is increased by the renal dysfunction caused by Cd toxicity. As a result, the bone mineral density of mother rat decreases significantly compared to that of normal lactating mother rat without Cd exposure.

It has been thought that Cd transport to the fetus is restrained by MT in the placenta (Goyer

1991; Goyer and Cherian 1992). However, in our study, Cd concentration in newborn rats (three days old) was high and dependent on the Cd exposure dose of mother rats. This suggests that a very small amount of Cd leaked from the placenta to the fetus, and was transported to the neonate through breast milk (Fig. 2, Ohta et al. unpublished data). Solaiman et al. (2001) also reported increased MT levels in the duodenum, kidney, and liver of lactating mouse.

It is not clear whether this decreased bone mineral density caused by Cd intake during lactation is substantially reversed during weaning. Further detailed studies are necessary to evaluate the effect of low-Cd intake on bone metabolism of the mother during pregnancy and lactation.

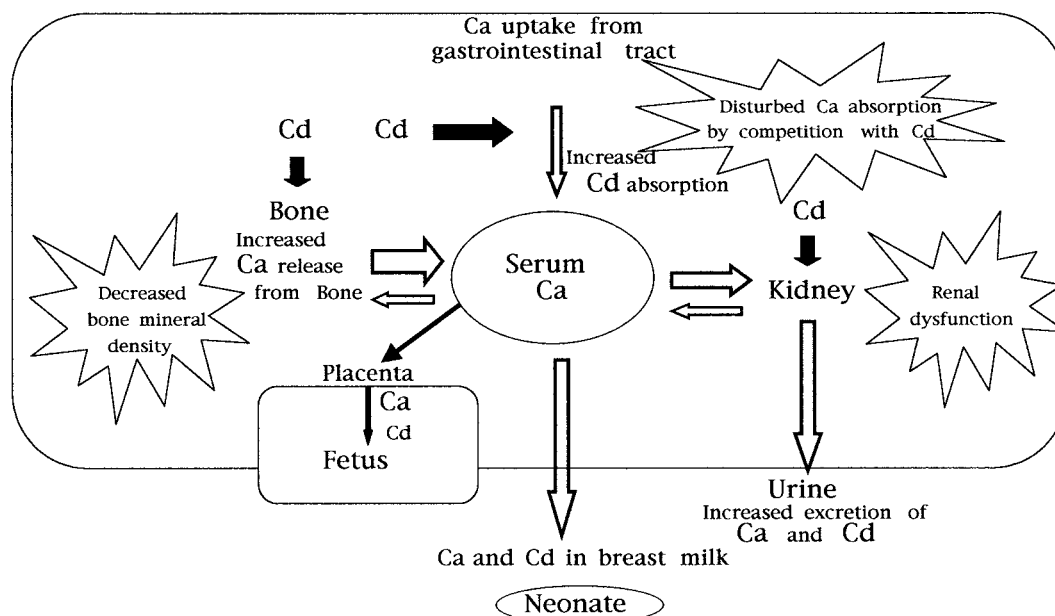


Fig. 2. Schematic illustration of Cd effects on Ca metabolism during lactation.

CONCLUSION

It is well known that renal dysfunction is a result of toxemia such as proteinuria, hypertension, and edema, and the dynamic changes in bone metabolism including Ca metabolism during pregnancy and lactation.

Similar to the case of normal pregnancy and lactation without Cd exposure, it is not known whether the decreased bone density of mother rat with chronic Cd intake is alleviated. In addition, the effect of Cd exposure on bone metabolism and renal function in cases of high frequencies of pregnancy and lactation is unclear.

To evaluate the effect of Cd at low intake levels on bone metabolism of mother rat during pregnancy and lactation under normal physiological conditions, further detailed studies are necessary. The effect of Cd on bone metabolism and renal function in humans should also be studied in the future.

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