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Dietary calcium supplementation to lower blood lead levels in pregnancy and lactation☆

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Abstract

Pregnancy and lactation are states known to be accompanied by physiologically upregulated bone resorption in response to the calcium demands of the developing fetus and nursing infant. The role of calcium supplements in altering maternal responses to fetal demand for calcium is not fully understood. Exposure to the toxicant lead is known to pose a major hazard to fetal neurodevelopment and growth. Since >95% of maternal lead is stored in the bone, mobilization of cumulative maternal lead stores into the circulation represents an endogenous source of exposure, which may pose a significant hazard for the fetus and infant. Maternal dietary calcium supplementation has been associated with reductions in lead levels in both animal and human studies when administered during pregnancy and lactation. Therefore, supplementation of the maternal diet with calcium may represent an important secondary prevention strategy aimed not only at reducing circulating levels of lead in the mother but also at reducing lead exposure to the developing fetus and nursing infant.

Keywords: Calcium; Diet; Supplementation; Lead; Pregnancy; Lactation; Review

1. Introduction

Despite overall declines in blood lead levels in the population [1,2], exposure to lead remains an international public health problem for at least three reasons. First, toxic effects are being identified at lower levels of exposure [3,4], apparently with no threshold [5,6], suggesting that any exposure may be harmful to the central nervous system. Second, exposed subgroups exist, and some — particularly children living in deteriorated housing [7], workers in several high-risk occupations [8], those living near hazardous wastes site or active smelters [9] and residents in countries still using leaded gasoline [10] — may be highly exposed. Finally, lead stores previously thought to be inert are actually mobilized to a marked degree [11–13], and previously accumulated bone lead stores may constitute an ongoing endogenous source of exposure, particularly during periods of heightened bone turnover [14,15].

2. Calcium requirements of pregnancy and lactation

Calcium requirements are increased substantially during pregnancy and lactation in order to meet the calcium needs of the developing fetus and nursing infant for skeletal mineralization and growth [16]. Profound changes in calcium metabolism and bone mineral status accompany pregnancy both during gestation and after delivery. Levels of calcium in plasma are under strict hormonal control [17] (Fig. 1). Calcium homeostasis is maintained by controlling intestinal calcium absorption, renal calcium excretion and mobilization of skeletal mineral stores. It is recommended that pregnant and nursing women adjust their dietary calcium intake to 1200–1500 mg/day, depending on their age [18]. The role of dietary calcium and mineral adequacy in skeletal changes during pregnancy and lactation is still controversial. The first half of pregnancy is a time of preparation for the demands of rapid fetal growth, which occurs at a later stage during which >90% of fetal growth

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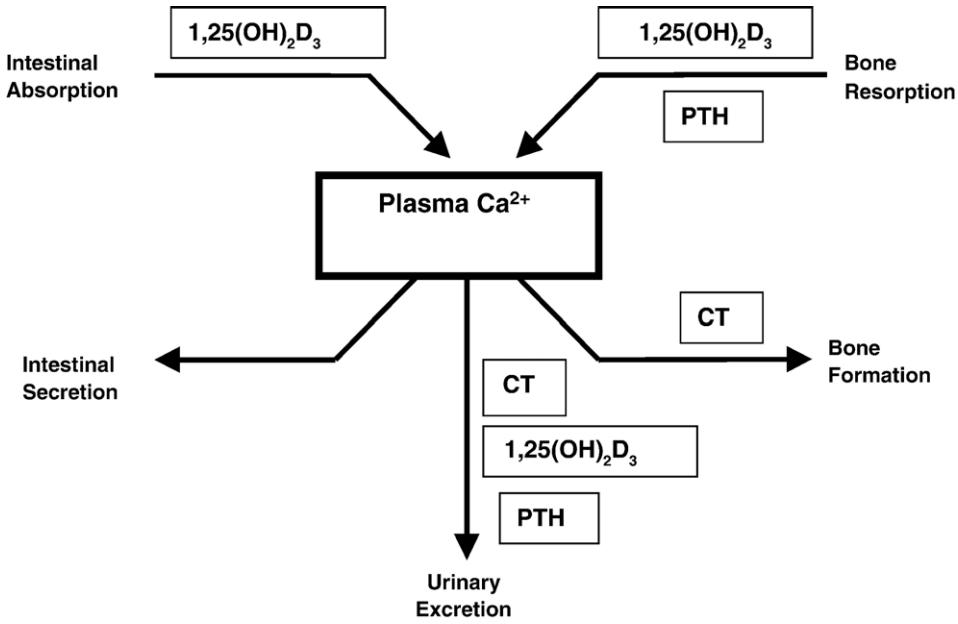

Fig. 1. Hormonal control of plasma calcium. PTH=parathyroid hormone; CT=calcitonin; 1,25(OH)2D3=vitamin D (adapted from Kovacs and Kronenberg [17]).

occurs, and calcium demand reaches about 300 mg/day in the last quarter of gestation [19]. During pregnancy, approximately 25–30 g of calcium is transferred to the fetus [20]. Lactation also has discernible effects on calcium homeostasis. Approximately 210 mg/day calcium is utilized for milk production during lactation [21]. Maternal calcium loss during lactation is estimated at 280–400 mg/day and can reach up to 1000 mg/day, which is approximately three times higher than that during pregnancy [22].

3. Pregnancy-associated and lactation-associated bone loss

Biochemical markers and bone density measurements indicate that bone resorption is increased during pregnancy and lactation [22]. The factors controlling skeletal changes during pregnancy and lactation are still largely unknown. In a study of bone loss in adolescent and adult pregnant women, the bone quantitative ultrasound index was 3.6% lower at 6 weeks postpartum than on entry into prenatal care [23]. Nulliparous patients had significantly greater bone loss than parous subjects. Bone loss observed during pregnancy and lactation appears to be transient, with levels returning to baseline after the return of ovarian function and cessation of nursing [24].

Sowers et al. [25], in a prospective study, found that women with a lactation duration of $\geq$6 months had mean bone mineral density losses of 5.1% and 4.8% at the lumbar spine and femoral neck, respectively. However, among women who breastfed for $\geq$6 months, there was evidence of return to baseline bone mineral density levels 12 months after parturition. The development of biochemical markers of bone turnover has increased the methods available to study bone metabolism. Markers of bone resorption [e.g., pyridinoline, deoxypyridinoline and cross-linked N-telopeptide (NTx)] are all breakdown products of Type I collagen. Using biochemical markers of bone formation and resorption, Black et al. [26] demonstrated significant increases in bone resorption and decreases in bone mineral density over the course of pregnancy, compared to prepregnancy levels. The increase in all bone resorption markers reached statistical significance by 14 weeks of gestation ($P<.02$) and continued to rise at a similar rate until 28 weeks ($P<.01$) before a marked increase up to 38 weeks of gestation ($P<.001$). In a case-crossover trial of calcium supplementation (1200 mg of calcium carbonate, at bedtime) during the third trimester of pregnancy, maternal bone resorption, as reflected by urinary NTx levels, was reduced by an average of 13.6 nM bone collagen equivalent (BCE)/mM creatinine (14%) in comparison to placebo [27], suggesting that dietary calcium plays a role in suppressing maternal bone mobilization.

4. Prenatal and early postnatal lead exposure

Mobilization of maternal bone lead stores released into the circulation during pregnancy and lactation constitutes a significant potential endogenous source of exposure to the mother, developing fetus and nursing infant [28] (Fig. 2). The decline in environmental sources of lead highlights the relevance of maternal bone as a continuing source of exposure. Women who were chronically exposed to environmental lead during infancy and adolescence may arrive at their reproductive years with a significant bone lead burden. Thus, bone lead represents an important threat not only to women with ongoing environmental exposures but also to women with reduced environmental exposures who

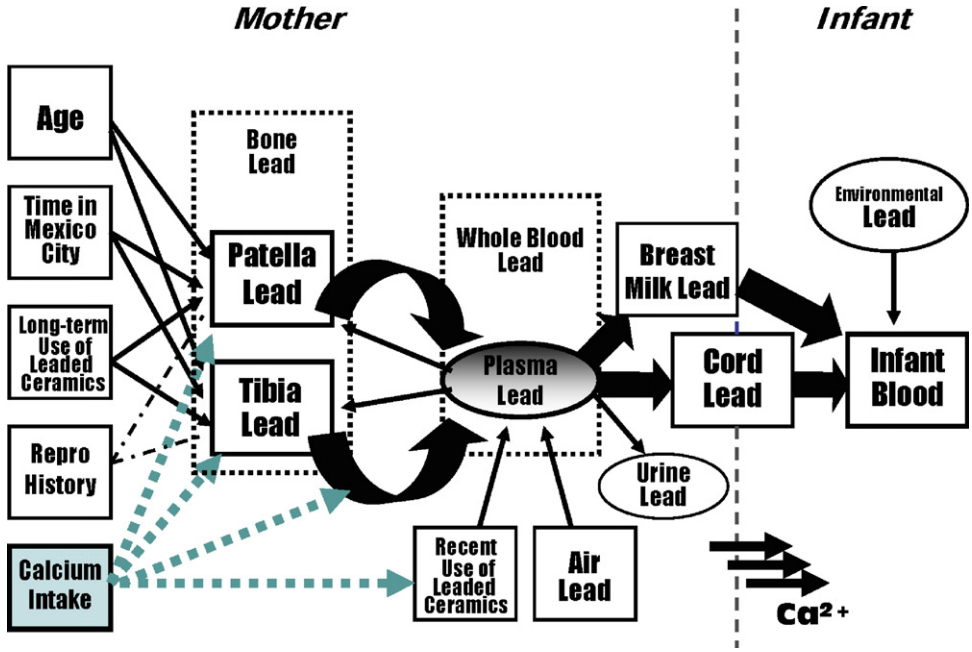

Fig. 2. Lead exposure pathway from mother to infant, using Mexico as an example (adapted from Chuang et al. [60]).

have had elevated exposures in the past [29]. This has serious consequences since lead mobilized from the bone goes directly into the plasma, which is the most biologically active compartment of lead that is available for crossing cell membranes [30]. Little is known about the direct contribution of endogenous exposures to toxic effects of lead, but given the incomplete blood–brain barrier in their developing nervous systems, children may be more susceptible to insults during the prenatal and early postnatal periods [31,32]. Lead freely crosses placental cell membranes by passive diffusion, and fetal blood lead concentration is highly correlated with maternal blood lead concentration [33]. Since approximately 95% of lead is stored in bones and mineralized tissues [34,35] and since bone lead has a half-life of years to decades [36], women and their infants will continue to be at risk for exposure long after environmental sources of lead have been abated.

5. Biokinetics of lead in pregnancy and lactation

Rothenberg et al. [37], attempting to model kinetics over the course of pregnancy, showed a significant drop in blood lead levels from Weeks 12 to 20. This drop is likely to be due, in large part, to hemodilution brought on by the rapid expansion of the plasma compartment during pregnancy (rather than a true drop in the mobilization of lead from the bone). However, from 20 weeks to delivery, they identified a significant increasing linear trend confirming the rise in blood lead levels in the later part of pregnancy. By examining the lead isotopic ratio in a small number of pregnant women who were recent immigrants to Australia (and pregnant Australian controls), Gulson et al. [38] were able to show that changes in skeletal contribution to blood lead increased over pregnancy. In addition, the mobilization of lead from the bone continued in the postpartum period up to 6 months during lactation at levels higher than those during pregnancy [11].

Hertz-Picciotto et al. [39] followed 195 women over the course of pregnancy and found a U-shaped pattern of maternal blood lead concentration across pregnancy. Late-pregnancy increases were steeper among women with low dietary calcium intake in both low-age and high-age groups. In another study in a smelter area with stable or decreasing environmental exposures, increases in blood lead levels, along with decreases in maternal calcium serum calcium levels, were observed during pregnancy [40]. Therefore, lead's effects may be more pronounced among those on calcium-deficient states.

6. Impact of dietary calcium on lead absorption and distribution

Dietary factors concurrent to the time of exposure are known to have an impact on lead dynamics, particularly with respect to the absorption of lead from the gastrointestinal tract [41,42], where nutrients may interact with lead through several potential mechanisms. Dietary nutrients potentially interact with lead by binding lead in the gut, competing with lead for absorption, altering intestinal cell avidity for lead or altering the affinity of target tissues to lead [43].

The potential role of nutritional status in altering susceptibility to lead exposure and toxicity has long been recognized [41,44]. There is increasing evidence suggesting that several nutrients may interact with lead absorption, deposition and excretion from the body. This may be particularly true at times, such as during pregnancy and

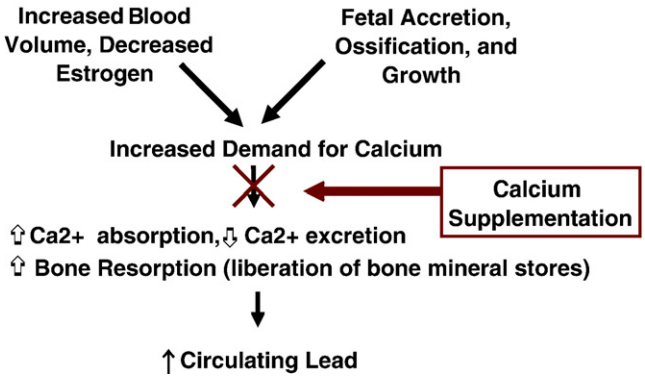

Fig. 3. Potential mechanism of calcium effects.

lactation, when nutrient requirements are increased in comparison to other periods of life. These relationships are of particular interest due to concern for fetal and infant exposure to circulating maternal lead.

Calcium deficiency has been shown to increase lead absorption [45] and lead retention [46]. There is also evidence supporting low dietary calcium and vitamin D as risk factors for elevated bone lead levels [47]. A higher milk intake during pregnancy has been associated with lower maternal and umbilical cord lead levels in postpartum women in Mexico [48], suggesting that calcium status may be an important factor in the maternal–fetal transfer of lead across the placenta. Calcium, phosphorus, magnesium, fluoride and vitamins D and K are known to be essential to bone health, but the effect of diet on the mobilization of previously accumulated bone lead stores between osseous and nonosseous tissues has not been fully investigated. Among postpartum women in Mexico City, lower levels of bone lead have been associated with a higher intake of calcium, vitamin D, phosphorus, magnesium iron, zinc and vitamin C, although these relationships showed inconsistent trends [49].

7. Lead effects on calcium and bone metabolism

Lead may also modify the metabolism of nutrients. Lead competes with calcium at calcium-binding sites and may subsequently alter protein function and calcium homeostasis [50]. There is also evidence that lead, like other divalent metal toxins, is an oxidative toxin that can both directly and indirectly cause cell damage [51]. Lead also impacts on a wide variety of biological activities at different intracellular levels at voltage-gated channels and on the first, second and third messengers [52]. Lead can substitute for calcium (Ca^{2+}) and zinc (Zn^{2+}) as a second messenger in ion-dependent events. In addition to being an important endogenous source of lead exposure, the bone may also be a target for toxic effects of lead [29,53]. Lead-induced changes in calcium-mediated cellular processes may affect skeletal development and regulation of skeletal mass [54]. More than 99% of total body calcium is found in teeth and bones, primarily in the form of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$]. Lead directly and indirectly alters many aspects of bone cell formation [54]. Lead is sequestered by the skeleton and incorporated into the hydroxyapatite matrix, where it remains until the bone has been remodeled. One study showed that calcium supplementation (~1 g/day) influenced the flux of lead released from the bone during late pregnancy and postpartum [55].

8. Effect of calcium supplementation on lead levels

In a randomized, double-blind, placebo-controlled trial, Hernandez-Avila et al. [56] showed that supplementation

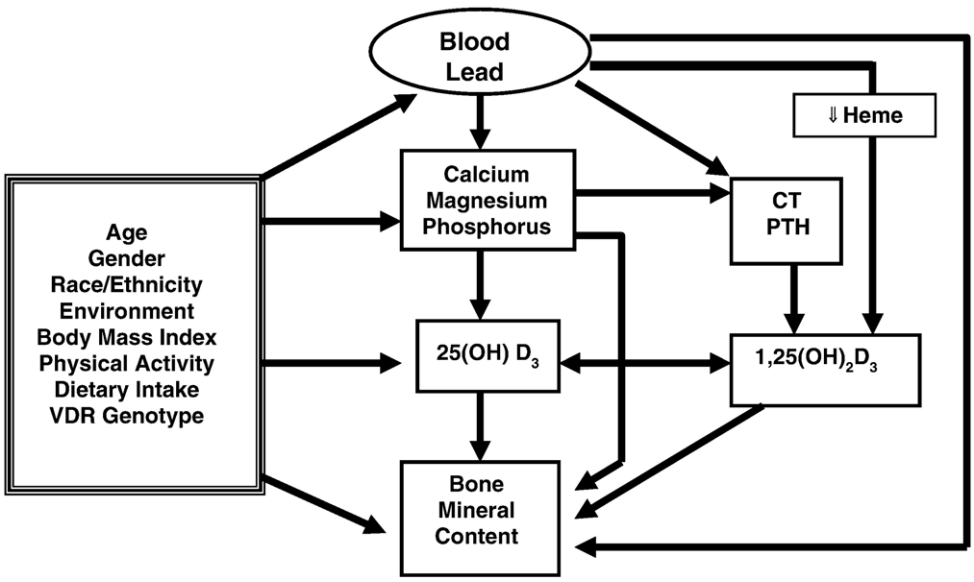

Fig. 4. Hypothesized effects of lead on calcium and vitamin D metabolism. PTH=parathyroid hormone; CT=calcitonin; 1,25(OH)2D3=1,25-dihydroxycholecalciferol (calcitriol), a hormonally active form of vitamin D; 25(OH)D3=circulating form of vitamin D.

with calcium carbonate (1200 mg of elemental calcium daily) among lactating women reduced maternal blood lead levels by 15–20% over the course of lactation. Compared with women who received the placebo, those who took supplements had a modest decrease in their blood lead levels over the study period at 3 months [−0.12 μg/dl; 95% confidence interval (95% CI)=−0.71 to 0.46 μg/dl] and at 6 months (−0.22 μg/dl; 95% CI=−0.77 to 0.34 μg/dl). The effect was more apparent among women who were compliant with supplement use and had high bone lead levels (patella bone lead >5 μg/g bone). Calcium supplementation was also associated with 5–10% lower breast milk lead levels among lactating women over the course of lactation [57].

During the second and third trimesters of pregnancy, calcium supplementation was associated with an average reduction of 19% in blood lead concentration in relation to placebo ($P<.001$) (Téllez-Rojo et al., submitted for publication) [58]. In addition, bone resorption was reduced by 13% in the supplement group in comparison to the placebo group ($P=.002$). Controlling for bone resorption rate (concentrations of NTx), the reduction of blood lead concentration related to the effect of the supplement was 15% ($P=.01$), in relation to placebo. This indicates that the effect of calcium may be exerted partially, although not entirely, by decreasing bone resorption and may also work by decreasing intestinal absorption or by increasing the excretion of lead from the circulation (Fig. 3).

9. Lead and the vitamin D receptor (VDR) gene

Lead absorption is inversely related to calcium stores. Therefore, a genetic polymorphism that modifies calcium absorption would be a reasonable candidate gene for modifying lead absorption and distribution. Since lead accumulates in the bone, another reasonable expectation is that a candidate gene would influence bone formation and resorption. One recent study suggests that the VDR *Bsm*I genotype may modify levels of lead in the bone, with subjects homozygous for the "B" allele (indicating the absence of restriction site) having increased tibia bone lead levels [59]. If this hypothesis is correct, then a population with physiologically up-regulated calcium absorption, such as pregnant and lactating women, may have higher blood lead levels and overall body burden if they carry the VDR *Bsm*I BB genotype (Fig. 4). Since calcium absorption is increased during pregnancy (and lactation), the activity/expression of vitamin D receptors is likely increased relative to other periods of life. These associations may be more pronounced among pregnant subjects, particularly in those with low dietary calcium intake. Previous work by our research group has demonstrated that maternal bone lead is a major determinant of umbilical cord lead level [60], which is an important biomarker of fetal exposure. Thus, VDR polymorphisms may also ultimately modify the association between maternal bone lead and umbilical cord lead (Ettinger et al., submitted for publication).

10. Conclusions

Calcium supplementation has been associated with modest reductions in blood lead levels when administered both during lactation and during pregnancy. This effect is likely related both to the suppression of maternal bone resorption (and consequent mobilization of lead stores in maternal bones) and to the suppression of the absorption of lead in dietary sources. Baseline dietary intake and levels of calcium supplementation in recent studies have been relatively low. It is possible that high levels of calcium are needed to counterbalance the nutritional needs of the developing fetus [61]. Other genetic, hormonal or lifestyle factors may also be responsible.

Dietary supplementation may constitute an important secondary prevention effort aimed not only at reducing circulating levels of lead in the mother but also at reducing lead exposure to the developing fetus and nursing infant. A better understanding of the potential for perinatal exposure — including lead kinetics and susceptibility in the pregnant and lactating mother, fetus and breastfeeding newborn — is needed for risk assessment and policy development. Since >95% of lead accumulates in long-lived bone stores, nutritional interventions may be an important strategy for preventing transgenerational exposures from lead-exposed women during their reproductive years.

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