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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 over 95% of maternal lead is stored in 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

Introduction

Despite overall declines in population blood lead levels (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).

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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)(Figure 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 1,200–1,500 milligrams per day depending on their age (18). The role of dietary calcium and mineral adequacy on skeletal changes of pregnancy and lactation is still controversial. The first half of pregnancy is a time of preparation for the demands of rapid fetal growth that occur in the later stage when >90% of fetal growth occurs and the calcium demand reaches about 300 mg/day in the last quarter of gestation (19). During pregnancy approximately 25 to 30 grams of calcium are transferred to the fetus (20). Lactation also has discernible effects on calcium homeostasis. Approximately 210 milligrams of calcium per day 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 1,000 mg/day which is approximately three times higher than during pregnancy (22).

Pregnancy- 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 of 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 at 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 and colleagues (25), in a prospective study, found that women with lactation duration of 6 months or longer had mean bone mineral density losses of 5.1% and 4.8% at the lumbar spine and femoral neck, respectively. However, among women who breast-fed for six months or longer, 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, 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 decreasing bone mineral density over the course of pregnancy compared to pre-pregnancy levels. The increase in all bone resorption markers reached statistical significance by 14 weeks gestation ($p<0.02$) and continued to rise at a similar rate until 28 weeks ($p<0.01$) before a marked increase up to 38 weeks gestation ($p<0.001$). In a case-crossover trial of calcium supplementation (1200 mg 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 BCE/mM creatinine (14%) in comparison to placebo (27) suggesting that dietary calcium plays a role in suppressing maternal bone mobilization.

Prenatal and Early Postnatal Lead Exposure

Mobilization of maternal bone lead stores released into circulation during pregnancy and lactation constitute a significant potential endogenous source of exposure to the mother, developing fetus and nursing infant (28)(Figure 2). The decline of 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 reproductive age 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 have had elevated exposures in the past (29). This has serious consequences since lead mobilized from bone goes directly to plasma which is the most biologically active compartment of lead available to cross cell membranes (30). Little is known about the direct contribution of endogenous exposures to the 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 bone and mineralized tissues (34,35), and 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.

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 rapid expansion of the plasma compartment during pregnancy (rather than a true drop in mobilization of lead from 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 and colleagues (38) were able to show that the changes in skeletal contribution to blood lead increased over pregnancy. In addition, the mobilization of lead from bone continued in the postpartum period for up to six months during lactation at levels higher than 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. The late pregnancy increases were steeper among women with low dietary calcium intake in both the low 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 during pregnancy were observed (40). Therefore, lead's effects may be more pronounced among those in calcium-deficient states.

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 by 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 by altering affinity of target tissues for 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 that suggests several nutrients may interact with lead absorption, deposition, and excretion of lead from the body. This may be particularly true at times, such as pregnancy and lactation, when nutrient requirements are increased in comparison to other periods of life. These relationships are of particular interest due to the 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). 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 non-osseous tissues has not been fully investigated. Among postpartum women in Mexico City, lower levels of bone lead were associated with higher intakes of calcium, vitamin D, phosphorus, magnesium iron, zinc, and vitamin C, though these relationships showed inconsistent trends (49).

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 homeostatis (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 the 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, bone may also be a target for the toxic effects of lead (29,53). Lead-induced changes in calcium-mediated cellular processes may affect skeletal development and regulation of skeletal mass (54). Over 99 percent 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, being incorporated into the hydroxyapatite matrix, where it remains until bone is remodeled. One study showed that calcium supplementation (~ 1 g/day) influenced the flux of lead released from bone during late pregnancy and postpartum (55).

Effect of Calcium Supplementation on Lead Levels

In a randomized, double-blind, placebo-control trial, Hernández-Avila et al. (56) showed that supplementation with calcium carbonate (1200 mg of elemental calcium daily) among lactating women reduced maternal blood lead levels 15–20% over the course of lactation. Compared with women who received the placebo, those who took supplements had a modest decrease of −0.12 μg/dL in their blood lead levels over the study period at 3 months (95% CI = −0.71 to 0.46 μg/dL) and −0.22 μg/dL at 6 months (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/gm 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 2nd and 3rd trimesters of pregnancy, calcium supplementation was associated with an average reduction of 19% in blood lead concentration in relation to placebo ($p<0.001$) (Téllez-Rojo, et al. Submitted)(58). Also, bone resorption was reduced by 13% in the supplement group in comparison to placebo ($p=0.002$). Controlling for bone resorption rate (concentrations of NTx), the reduction of the blood lead concentration related to the effect of the supplement was 15% ($p=0.01$), 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 be working by decreasing intestinal absorption or increasing excretion of lead from circulation (Figure 3).

Lead and the Vitamin D Receptor Gene

Lead absorption is inversely related to calcium stores. Therefore, a genetic polymorphism that modifies calcium absorption would be a reasonable candidate gene to modify lead absorption and distribution. Since lead is accumulated in bone, another reasonable expectation is that a candidate gene would influence bone formation and resorption. One recent study suggests that the VDR BsmI genotype may modify levels of lead in bone, with subjects homozygous for the "B" allele (indicating absence of the restriction site) having increased tibia bone lead levels (59). If this hypothesis is correct, then a population with physiologically-upregulated calcium absorption, such as pregnant and lactating women, may have higher blood lead levels and overall body burden if they carry the VDR BsmI BB genotype (Figure 4). Since calcium absorption is increased during pregnancy (and lactation), the activity/expression of vitamin D receptors is likely increased relative to other periods in 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)

Conclusions

Calcium supplementation has been associated with modest reductions in blood lead levels both when administered during lactation and during pregnancy. This may effect is likely related both to the suppression of maternal bone resorption (and consequent mobilization of lead stored in maternal bone) as well as 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. Better understanding of the potential for perinatal exposure, including lead kinetics and susceptibility in the pregnant and lactating mother, fetus, and breast-feeding newborn, is needed for the risk assessment and policy development. Since over 95% of lead is accumulates in long-lived bone stores, nutritional interventions may be an important strategy for preventing trans-generational exposures from lead-exposed women during the reproductive years.

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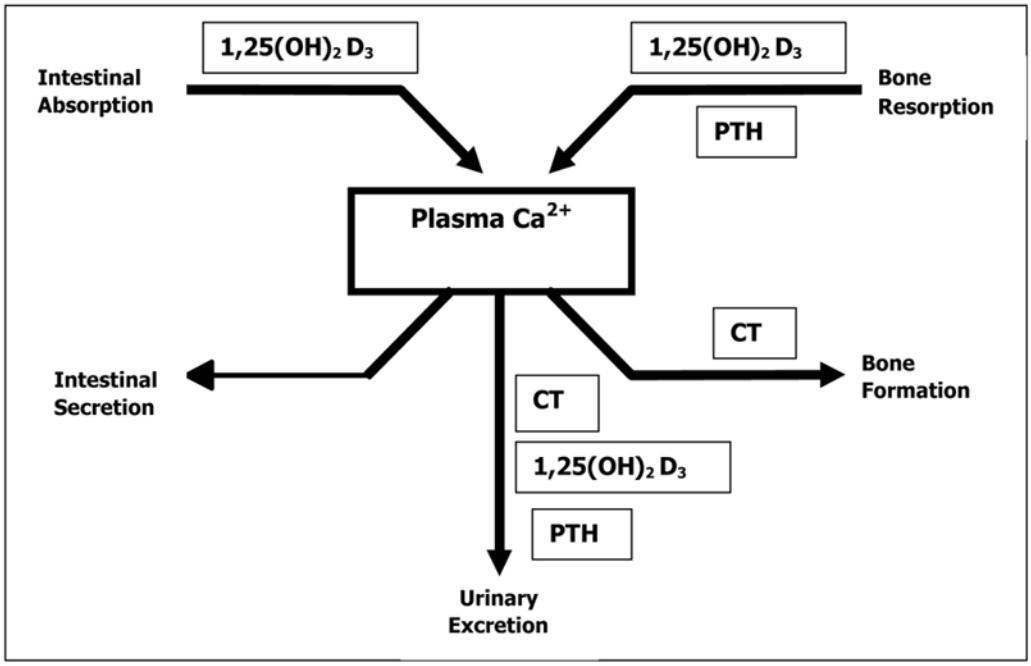

Figure 1. Hormonal Control of Plasma Calcium

Note: PTH=parathyroid hormone; CT=calcitonin; 1,25(OH)2D3=vitamin D (Adapted from: Kovacs & Kronenberg, 1997)

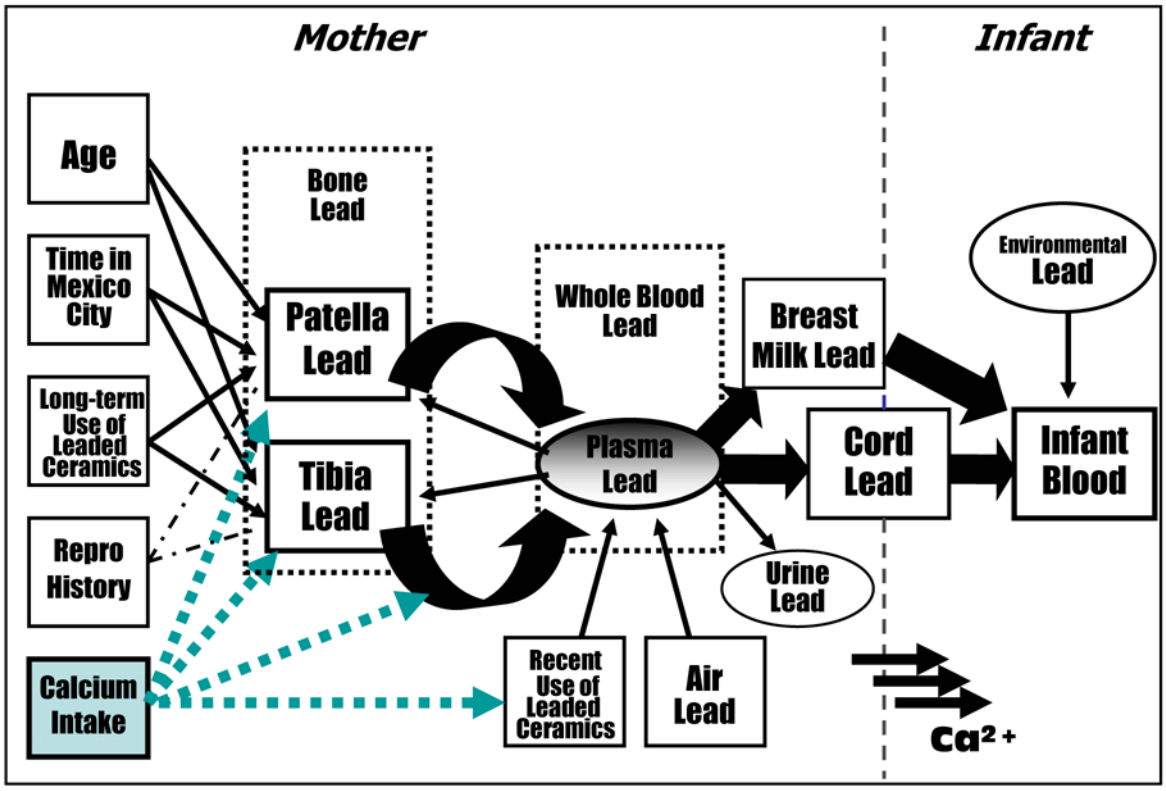

Figure 2.
Lead Exposure Pathway from Mother to Infant (using Mexico as an example; adapted from Chuang et al., 2001).

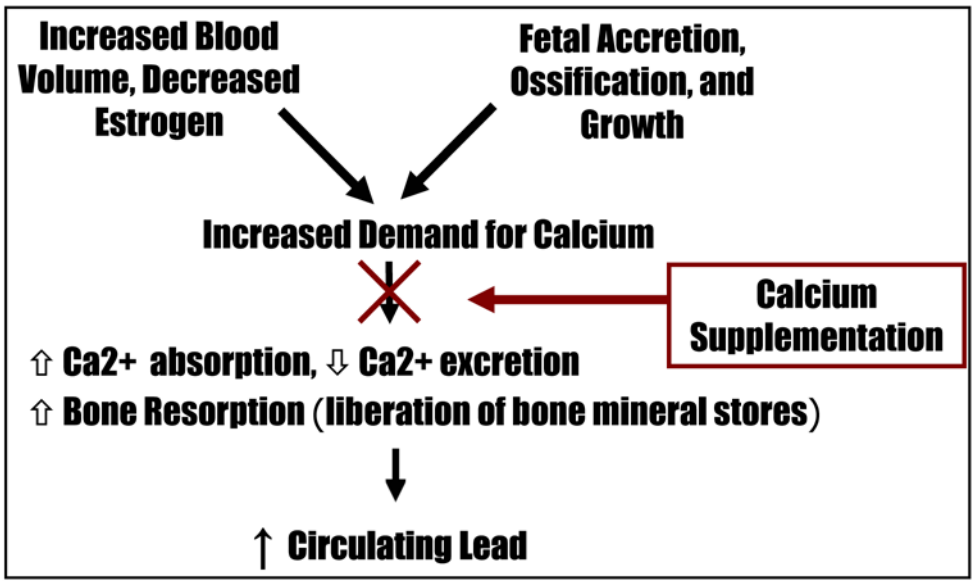

Figure 3.
Potential Mechanism of Calcium Effects

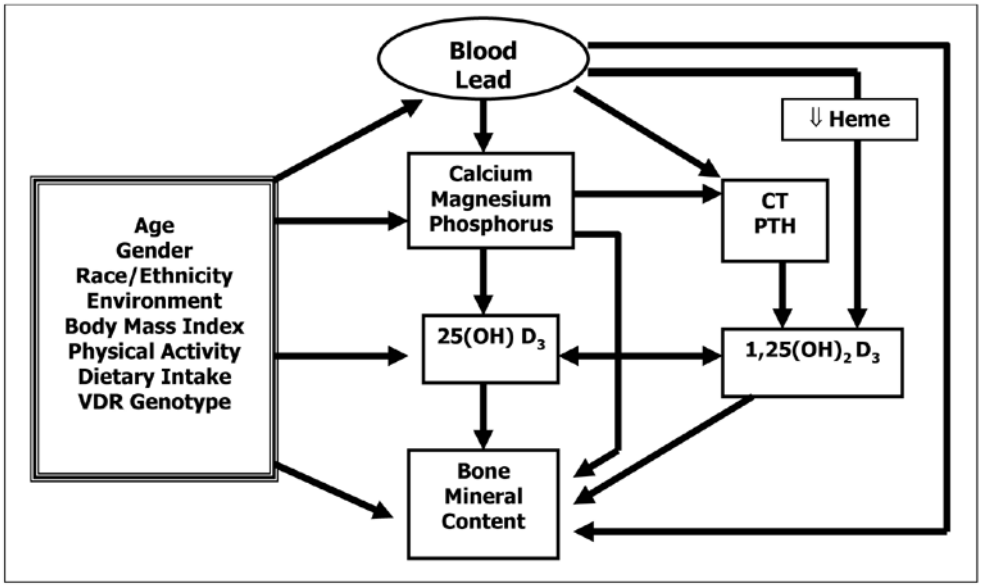

Figure 4. Hypothesized Effects of Lead on Calcium and Vitamin D Metabolism

Note: PTH=parathyroid hormone; CT=calcitonin; 1,25(OH)2D3=1,25-dihydroxycholecalciferol (calcitriol) hormonally-active form of vitamin D; 25(OH) D3=circulating form of vitamin D