Relationship of Blood and Bone Lead to Menopause and Bone Mineral Density among Middle-Age Women in Mexico City

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To describe the relationship of blood lead levels to menopause and bone lead levels, we conducted a cross-sectional study on 232 pre- or perimenopausal (PreM) and postmenopausal (PosM) women who participated in an osteoporosis-screening program in Mexico City during the first quarter of 1995. Information regarding reproductive characteristics and known risk factors for blood lead was obtained using a standard questionnaire by direct interview. The mean age of the population was 54.7 years (SD = 9.8), with a mean blood lead level of 9.2 µg/dL (SD = 4.7/dL) and a range from 2.1 to 32.1µg/dL. After adjusting for age and bone lead levels, the mean blood lead level was 1.98 µg/dL higher in PosM women than in PreM women (p = 0.024). The increase in mean blood lead levels peaked during the second year of amenorrhea with a level (10.35 µg/dL) that was 3.51 µg/dL higher than that of PreM women. Other important predictors of blood lead levels were use of lead-glazed ceramics, schooling, trabecular bone lead, body mass index, time of living in Mexico City, and use of hormone replacement therapy. Bone density was not associated with blood lead levels. These results support the hypothesis that release of bone lead stores increases during menopause and constitutes an internal source of exposure possibly associated with health effects in women in menopause transition. *Key words:* **blood lead, bone lead, bone mineral density, menopause, Mexico.** *Environ Health Perspect* **111:631–636 (2003). doi:10.1289/ehp.5149 available via** *http://dx.doi.org/* **[Online 16 December 2002]**

For decades the population of Mexico City was exposed to high environmental lead levels because of the combustion of leaded gasoline and poor environmental control of industrial activities. However, this situation changed in 1986 with regulatory actions that reduced the lead emissions and lead content of gasoline, culminating in its elimination in 1997 (Hernández-Avila et al. 2000). Similar regulatory actions were established for other sources of lead exposure such as paints, solders in canned food, and cosmetics. In addition, in 1995 the Mexican government initiated the search for alternative substitute for lead used in low-temperature hand-made ceramics, but at present this type of ceramic remains the main nonoccupational source of lead exposure in Mexico (Hernández-Avila and Romieu 1991; Romieu et al. 1994).

Lead from environmental and occupational sources enters the body through inhalation of particles or intake of lead-contaminated food (Lockitch 1993). It is transported by blood to soft tissues, where it remains for short periods and is finally deposited in bone tissue (Barry and Mossmann 1970). More than 90% of the lead present in the body is stored in bones throughout life, where it may remain for decades (Barry and Mossmann 1970). Nevertheless, bone tissue does not represent a site of permanent sequestration of lead but rather a source of continuous internal exposure that may increase as a result of the changes in bone turnover observed at different life stages (Gulson et al. 1995; Pounds et al. 1991). This may be the case with menopause, where bone mass loss is a frequent phenomenon that typically starts in the perimenopausal years and continues with an accelerated loss in the early postmenopausal years (Cummings et al. 1985; Elders et al. 1988; Nilas and Christiansen 1988; Riggs and Melton 1986; Ruegsegger et al. 1984; Silbergeld et al. 1993).

Although previous studies demonstrated the blood lead increase during this stage of life (Muldoon et al. 1994; Silbergeld et al. 1988; Symansky and Hertz-Picciotto 1995; Weyerman and Brenner 1998), only one study recently published simultaneously measured lead levels in blood and bone among perimenopausal women (Korrick et al. 2002).

The objective of this study was to examine the relationship between blood and bone lead during menopause under the hypothesis that postmenopausal (PosM) women have higher blood lead levels in comparison with premenopausal women after controlling for bone lead content, age, and exposure to environmental sources. A second hypothesis is that higher bone remodeling rates among PosM women—using bone mineral density (BMD) as an indicator—is associated with higher blood lead levels after controlling for age and bone lead among other variables.

Materials and Methods

The study population was recruited from women attending an osteoporosis-screening program carried out by the Mexican Committee for Osteoporosis Research in Mexico City. Women were recruited through conferences given live during a radio program aimed at women. During the program, one of us (J.T.O.), an expert in osteoporosis, explained to the audience a set of actions to prevent osteoporosis and provided information regarding its diagnosis and treatment and the screening program. The radio programs were broadcast during the first quarter of 1995, and a total of 961 women were recruited. Once the clinical procedures necessary for osteoporosis diagnosing were carried out, all participants were invited for complimentary measurements of blood and bone lead levels. A total of 653 women consented to the blood lead test, and 35% of these (n = 232) completed measurements of both blood and bone lead. The primary reason for not completing the bone lead measurement was the inconvenience of particiants visiting a different clinic far from the initial enrollment and screening center. For the analyses, the final sample was made up of these 232 women, of whom 36 were pre- or perimenopausal (PreM) and 196 were PosM.

The research protocol was approved by the Human Subjects Committee of the National Institute of Public Health of Mexico. All participants gave their informed consent and received a detailed explanation of the study and procedures used, as well as counseling on how to reduce lead exposure.

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We used a structured questionnaire that collected information on sociodemographics, life styles, reproductive history, and sources of environmental exposure to lead. The education level of the subjects was grouped in the following three categories: less than primary school, primary and secondary school, and high school or more. We also asked about tobacco consumption, alcohol consumption, and physical exercise. With regard to tobacco, the subjects were classified according to current smoking habits. Alcohol consumption was analyzed according to frequency (abstainers, less then once a month but at least once a year, from two to three times a month, and one or more times a week) and the number of drinks consumed per occasion. Regarding physical activity, participants were asked whether they currently exercised on a regular basis. In the section of reproductive characteristics, we collected information on the use of exogenous hormones and the time of their use, either for family planning purposes or to treat symptoms associated with menopause. Other variables included the number of pregnancies overall, the number of deliveries, total period of breast-feeding (in months), type of menopause (natural or surgical), and years since menopause.

Table 1. Characteristics of women participating in the study according to their distribution in participation groups.

	Participated in the bone lead screening test		
Variables	Yes	No	*p*-Value
Age (years)			
n	232	421	
Mean	54.1	53.3	0.33
Blood lead (μg/dL log-e)			
n	232	421	
Mean	9.2	10.0	0.004
Height (cm)			
n	222	406	
Mean	154.7	153.9	0.09
Weight (kg)			
n	222	406	
Mean	64.5	62.2	0.01
Lumbar spine (μg/cm^2)			
n	221	405	
Mean	1.022	1.035	0.64
Femoral neck (μg/cm^2)			
n	220	402	
Mean	0.873	0.881	0.46
No. of pregnancies			
n	232	421	
Mean	4.2	4.1	0.53
Use of lead-glazed ceramics			
Yes	49	99	
No	183	322	0.48
Literacy (years of school)			
0–5	27	54	
6–9	154	267	
≥ 10	51	99	0.51
Smoking (%)			
Yes (current)	42	64	
Yes (past)	45	62	0.58
Never	145	278	

Women were classified as menopausal according to their answers to the following questions: Do you continue menstruating (yes/no)? If you have stopped menstruating, how long have you not been menstruating (number of months)? Have you stopped menstruating in the natural way, because of some disease, pregnancy or lactation, or because you underwent surgery? The menopause event was considered positive when the subjects were in amenorrhea for 12 months not due to pregnancy, lactation, or any disease or surgical procedure. Finally, menopause was classified as natural or surgical. Years since menopause was calculated as the time since the last menstrual period or time since hysterectomy. The questionnaire also included a section to identify sources of environmental and indoor exposure to lead. Among them, the following were identified: type of vehicular traffic next to the place of residence (intense, intermediate, or low), residence time (in years) in Mexico City, and overall time spent in preparing and storing food in lead-glazed ceramics. These characteristics represent the most important sources of lead exposure previously identified in our population (Hernández-Avila and Romieu 1991; Romieu et al. 1994).

Lead measurements. Blood samples were analyzed with a graphite furnace atomic absorption spectrophotometry instrument (Perkin Elmer 3000; Perkin Elmer, Norwalk, CT) at the metals laboratory of the American British Cowdray Hospital in Mexico City. The laboratory standardization program of the Wisconsin State Laboratory of Hygiene (Madison, WI) provided external quality control specimens varying from 2 to 88 μg/dL. Our laboratory maintained acceptable precision and accuracy during the study time (correlation = 0.98; mean difference, 0.71 μg/dL; SD = 0.68).

Bone lead measurements were taken of each subject's midtibial shaft (cortical bone) and patella (trabecular) using a spot-source ^{109}Cd KXRF instrument constructed at Harvard University and installed in a research facility at the American British Cowdray Hospital. Physical principles, technical specifications,

Table 2. Study population according to selected variables.

Variables	*n*[a]	Percentages or means and SD values	Range
Age (years)	232	54.1 ± 9.8	28–88
Literacy (%)			
0–5 years	27	11.6	
6–9 years	154	66.4	
≥ 10 years	51	22.0	
Height (cm)	222	154.7 ± 5.8	1.43–1.82
Weight (kg)	222	64.5 ± 10.9	44–105
Body mass index	222	27.1 ± 4.6	17.3–35.8
Blood lead (μg/dL)	232	9.2 ± 4.7	2.1–32.1
Patella lead (μg Pb/g bone mineral)	232	22.73 ± 14.9	ND–89.3
Tibia lead (μg Pb/g bone mineral)	232	14.85 ± 10.1	ND–57.8
Smoking (%)			
Yes (current)	42	18.1	
Yes (past)	45	19.3	
Never	145	62.6	
Physical activity (%)			
Yes	128	55.2	
No	104	44.8	
No. of drinks per week (%)			
One or less	127	54.7	
Two	55	23.7	
Three or more	50	21.6	
Use of lead-glazed ceramics			
Yes	49	21.1	
No	183	78.8	
Menarche (mean age)	232	12.7 ± 1.5	9–17
No. of pregnancies	232	4.26 ± 2.6	0–13
History of breast-feeding (%)			
Yes	187	80.6	
No	26	11.2	
Nulliparous	19	8.2	
Premenopausal or perimenopausal	36	15.5	
Postmenopausal	196	84.5	
Surgical	76	32.8	
Natural	120	51.7	
Age at menopause	196	45.3 ± 7.0	24–60
Years since menopause	191	11.3 ± 8.7	1–42
BMD lumbar spine (g/cm^2)	221	1.022 ± 0.18	0.47–1.62
BMD femoral neck (g/cm^2)	220	0.873 ± 0.14	0.54–1.31

[a]Some variables have missing values.

validation, and use of this and other KXRF instruments have been described in detail elsewhere (Aro et al. 1994; Hu et al. 1995).

In brief, the instrument uses a ^{109}Cd γ-ray source to provoke the emission of fluorescent photons from target tissue that are then detected, counted, and arrayed on a spectrum. Net lead signal is determined after subtraction of Compton background counts by a linear least-squares algorithm. The lead fluorescent signal is then normalized to the elastic or coherently scattered γ-ray signal, which arises predominantly from the calcium and phosphor present in bone mineral. For the present study, 30-min measurements were taken at the midshaft of the left tibia (cortical bone) and at the left patella (trabecular bone) after each region had been washed with a 50% solution of isopropyl alcohol. The instrument provides an estimate of the uncertainty associated with each measurement; for purposes of quality control of bone lead measurements, we excluded 14 individuals with questionable values either because the movement of the limb being measured was out of the measurement field or because of the extreme thickness of overlying tissue, which resulted in estimates of uncertainty greater than 10 μg Pb/g bone mineral for the tibia or 15 μg Pb/g for the patella. The mean uncertainty (and SD) for patella and tibia in our study were 8.4 (2.8) and 6.9 (3.1), respectively.

BMD was measured at the lumbar spine and femur neck with a LUNAR DEXA (dual energy x-ray absorptiometry) densitometer (GE Lunar Corp., Madison, WI). On initiating each measuring session, the equipment was calibrated by standardized mineral density devices (photons) whose coefficients of variation were lower than 4%. The results are expressed in grams per square centimeter. We used the criteria established by the World Health Organization (WHO 1994) for BMD classification: *a*) normal, if BMD value was greater than at least 1 SD in relation to the reference group; *b*) osteopenia, if BMD was between –1.0 and –1.5 SD values; and *c*) osteoporosis, if BMD was lower than –2.5 SD values in relation to the reference group (WHO 1994).

We performed an exploratory analysis of each variable included in the study by univariate statistics and distribution plots. The bivariate analysis included test (two groups) and analysis of variance (three or more groups); linear regression models were used to examine the relationship between blood lead levels and variables of interest. The age effect was modeled using linear and quadratic terms to account for nonlinear relationships observed between age and blood lead (Hernández-Avila et al. 2000; Silbergeld et al. 1988).

First, the relationship between each variable and log-e (natural log) transformation of blood lead levels was examined. Then, we analyzed the relationship between blood lead and all those variables that in bivariate analysis would have achieved 0.15 significance level. We defined the best model by dropping covariates one by one from a saturated model that included all variables with a p-value below 0.15. Our final multivariate model included all-important predictors with a statistically significant association defined at $p < 0.10$.

When bone lead concentrations are very low (< 5 μg/g bone mineral), the K-XRF measurements may provide negative values because of the algorithm used by equipment software (Hu et al. 1995). To test the robustness of our findings in relation to negative values, these were randomly distributed within an interval between 0 and 5 μg Pb/g of bone mineral. Reanalysis using these values did not change the estimates of interest. All statistical analysis procedures were carried out with a Stata package (Stata Statistical Software, release 7.0, Stata Corp., College Station, TX).

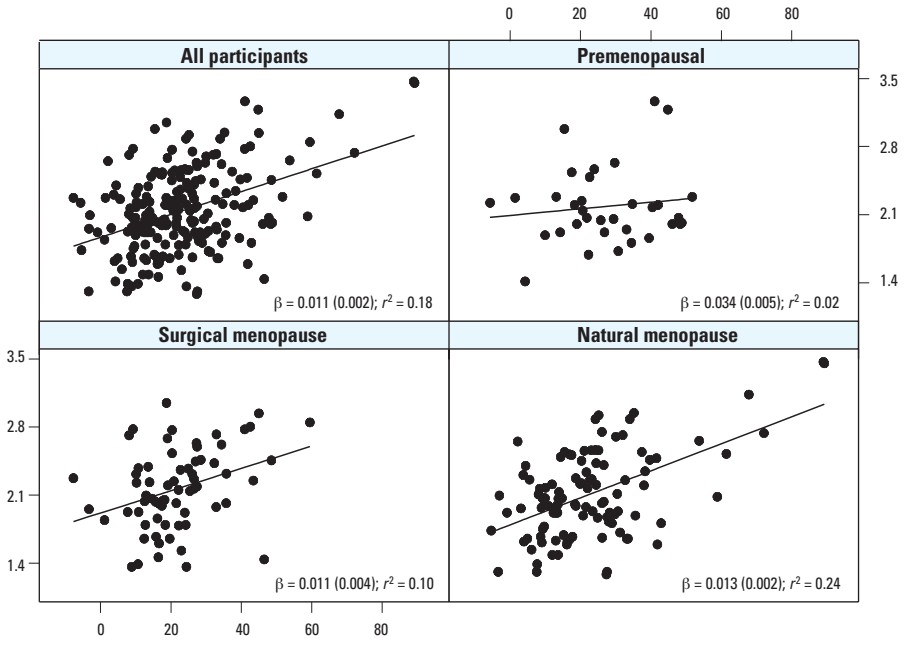

Figure 1. Regression analysis between blood lead levels (micrograms per deciliter, log-e transformed) and patella bone lead levels (μg Pb/g bone mineral) for all participants and subgroups divided according to menopausal status.

Results

The study group (n = 232) showed no differences in relation to nonparticipants regarding most characteristics of interest (Table 1). Women who participated showed a lower mean blood lead concentration and a higher body weight.

The group of PreM women constituted 15.5% of the total population. The age of the population ranged from 28 to 88 years, with a mean of 54.7 years (SD = 9.8). Most of these women (66.4%) had an intermediate level of schooling (6–9 years). Regarding reproductive characteristics, 92% had a history of one or more pregnancies (mean 4.3, SD = 2.6), and 81% had breast-fed their infant. The mean age of natural menopause was 47.6 years (SD = 5.8) and of surgical menopause was 42.2 years (SD = 6.7). About 46% of the participants with menopause reported the use of hormone replacement therapy (HRT).

Life-style characteristics were as follows: 18% of the participants were classified as current smokers; 55% exercised on a regular basis; 22% consumed three or more alcoholic drinks per occasion, and 23% prepared meals in lead-glazed ceramic cookware during the last week. Blood lead levels were distributed between a minimum value of 2.1 μg/dL and a maximum of 32.1 μg/dL, with a mean of 9.2 μg/dL (SD = 4.71) and a 95% confidence interval of 8.5–9.8 μg/dL. Lead values in trabecular and cortical bone were distributed with means of 22.7 μg Pb/g of bone mineral (SD = 14.9) and 14.9 μg Pb/g (SD = 10.09), respectively (Table 2). Lead levels in trabecular bone (patella) explained an important percentage of blood lead variation (r^2 = 18%). For each 1 μg Pb/g of bone mineral, blood lead levels increased by 1.1% (regression coefficient 0.011; p = 0.001). However, this association varied significantly ($p < 0.01$) when we stratified according to type of menopause (Figure 1). Blood lead increased by 0.3 and 1.1% per μg Pb/g of bone mineral, for PreM and PosM women, respectively. According to this model, a change of 10 μg Pb/g of bone mineral in PosM will be associated with an increase in blood lead of 1.4 μg/dL, whereas a similar change among PreM women will be associated with an increase of 0.8 μg/dL.

Table 3. Blood lead levels (microgram/deciliter) according to sociodemographic, life style, and reproductive characteristics.

Variables	*n*	Mean	SD	*p*-Value[a]	Means adjusted by age and bone lead	Adjusted *p*-value[a]
Age groups (years)						
< 40	12	10.5	5.5	0.23	9.7	0.19
40–44	23	9.4	4.1		9.1	
45–49	41	10.6	6.0		10.4	
50–54	40	9.1	3.9		9.2	
55–59	49	8.5	3.0		9.1	
60–64	30	8.9	5.5		8.8	
65–69	19	8.3	6.4		8.4	
≥ 70	18	7.7	3.2		7.5	
Literacy (years of school)						
0–5	27	10.2	5.7	0.06	10.9	< 0.01
6–9	154	9.3	4.7		9.2	
≥ 10	51	8.1	4.1		8.1	
No. of pregnancies						
None	19	9.7	5.7	0.42	9.8	0.24
1–3	82	8.5	3.2		8.4	
4–6	87	9.0	4.4		9.1	
≥ 7	44	10.4	6.7		10.4	
Breast-feeding						
No	26	8.2	3.2	0.43	8.26	0.38
Yes	187	9.2	4.8		9.21	
Menopause						
No (PreM)	36	9.4	4.9	0.69	7.5	0.02
Yes (PosM)	196	9.1	4.7		9.5	
Type of menopause						
PreM	36	9.4	4.9	0.50	7.4	0.08
Surgical	76	9.3	3.8		9.4	
Natural	120	9.00	5.2		9.5	
Time since menopause (surgical, months)						
PreM	36	9.4	4.9	0.32	8.2	0.15
12	9	11.2	4.5		11.2	
13–24	6	11.1	3.9		9.9	
25–36	10	7.5	2.7		8.2	
37–48	9	8.9	3.6		9.3	
≥ 49 years	42	9.1	3.7		10.1	
Time since menopause (natural, months)						
PreM	36	9.4	4.9	0.23	6.8	0.06
12	15	9.3	4.3		7.9	
13–24	18	9.7	4.5		10.4	
25–36	12	6.8	2.5		7.2	
37–48	12	11.2	7.2		11.4	
≥ 49 years	58	8.9	5.6		10.3	
HRT						
Yes	91	8.5	3.5	0.20	8.8	0.10
No	105	9.7	5.5		10.1	
HRT (natural menopause)						
Yes	53	7.5	3.1	< 0.01	8.4	0.01
No	67	10.2	6.1		10.5	
HRT (surgical menopause)						
Yes	38	9.8	3.7	0.14	9.4	0.41
No	38	8.7	3.1		9.1	
Smoking						
Yes (current)	42	9.1	4.9	0.74	8.3	0.10
Yes (past)	45	8.0	4.8		8.4	
Never	145	9.5	4.6		9.4	
Physical activity						
Yes	128	9.6	5.2	0.09	9.5	0.14
No	104	8.6	3.9		8.6	
No. of drinks						
One or less	127	8.7	4.7	0.112	8.9	0.20
Two	55	9.9	5.6		9.9	
Three +	50	9.4	3.6		8.9	
Use of lead-glazed ceramics						
Yes	49	10.7	6.7	< 0.01	10.5	< 0.01
No	183	8.6	3.6		9.2	

[a]*p*-Value from ANOVA using log-e transformed blood lead as the dependent variable.

BMDs of lumbar spine and femur neck were distributed with means of 1.022 µg/cm^2(SD = 0.177) and 0.873 µg/cm^2 (SD = 0.135), respectively. We did not find any relationship between blood lead values and BMDs of lumbar spine and femur neck. Regression coefficient for BMD of lumbar spine was 0.0048 (p = 0.962), and for femur neck was 0.1561 (p = 0.217). These coefficients were not modified after adjusting for age and bone lead.

No linear relationship was observed between blood lead levels and age (p = 0.23). The highest mean blood lead was observed for the 45- to 49-year-old group, corresponding to the mean age of natural menopause, when it reached a mean concentration of 10.6 µg/dL and progressively decreased to values smaller than those found in PreM women.

In the baseline multivariate model that adjusted for age and bone lead (Table 3), PosM women showed blood lead levels 1.98 µg/dL higher than those found in PreM women (p = 0.024). This increase was apparent for women with surgical menopause (1.91 µg/dL) and women with natural menopause (2.1 µg/dL) compared with that for PreM women. In relation to the years since menopause, the distribution of blood lead values showed two points of inflection that, in the case of women with surgical menopause, corresponded to the first and fifth year after menopause (11.17 and 10.07 µg/dL), which corresponded to a difference of 3.35 and 1.92 µg/dL compared with those in the PreM group (p = 0.158); for women with natural menopause, the two points of inflection corresponded to the second and fourth year after menopause (10.35 and 11.43 µg/dL), differences of 2.2 and 3.28 µg/dL, respectively (p = 0.063).

PosM women who used HRT (adjusting for age and bone lead) had lower blood lead levels than PosM women who did not use the therapy, with an estimated mean blood lead difference of –1.25 µg/dL (p = 0.09). When the analysis was restricted to the group of participants with natural menopause, the mean blood lead concentration was 2.64 µg/dL higher in the group of PosM women who were nonusers of replacement estrogens (p = 0.005).

The use of lead-glazed ceramics was an important predictor of blood lead levels. The women who prepared and stored food in lead-glazed ceramic cookware during the previous week showed higher blood lead compared with those who did not use it, with differences of 2.48 and 2.01 µg/dL, respectively (p < 0.05).

Finally, the most parsimonious multivariate model that explained 38.7% of the variation in blood lead levels included the following variables: age (linear and quadratic terms), time of

postmenopause, body mass index, patella lead, use of lead-glazed ceramic cookware, schooling level greater than 6 years, and time of living in Mexico City (Table 4).

Discussion

Our results showed that blood lead increases significantly in the PosM period and particularly in the first 3 years of this period. Our data suggest that once these maximum levels are achieved, the blood lead decreases in the third year and afterward starts increasing again. This finding is consistent with a particular bone remodeling pattern during the first years of postmenopause that mainly depends on higher bone turnover of trabecular bone. As is well known, the trabecular bone loss increases in the perimenopausal period, which is followed by an accelerated loss in the first years of postmenopause, and then bone resorption decreases and becomes constant (Cummings et al. 1985; Elders et al. 1988; Nilas and Christiansen 1988; Riggs and Melton 1986; Ruegsegger et al. 1984).

As reported by Muldoon et al. (1994), our study did not find high blood lead levels in women with low mineral density. Measurements of BMD in cross-sectional studies provide a snapshot of the balance between bone deposition and bone resorption rates over preceding years, whereas blood lead levels would be expected to depend more specifically on absolute rates of ongoing bone resorption. Because of this limitation Hu et al. (1998) proposed the use of bone markers that are specific for ongoing rates of bone resorption such as the N-telopeptide of type I collagen (urinary NTX). Recent research in elderly men suggests that urinary NTX is a significant modifier of the bone lead–blood lead relationship.

The age-adjusted difference in trabecular bone lead concentrations observed between PosM and premenopausal women (difference of –5.8 μg of lead per gram of bone mineral; $p = 0.02$) supports the hypothesis that the lead is mobilized from the bone compartments toward the circulation and contributes to the increase of blood lead levels in this stage of life. The hypothesis is also supported by our observation that the use of replacement estrogens was also associated with lower blood lead levels among PosM women. Furthermore, patella lead explained the greatest part of variations in blood lead levels, and its independent effect remained the same after controlling other important predictors of blood lead. A different pattern was found in the association between tibia lead and blood lead. These levels were marginally different between PreM and PosM women ($p = 0.06$). This difference suggests the existence of lead pools in the mineral tissue (trabecular represented by patella and cortical by tibia) that follow different turnovers. In cortical bone, it is known that its turnover is much slower than that occurring in trabecular bone, so its contribution to blood lead levels is expected to be smaller. It should be noted, however, that cortical bone composes the majority of skeletal mass (~80%), making even modest resorption of cortical bone a potentially major influence on blood lead levels. Similar results were reported by Kosnett et al. (1994) in women older than 55 years. Silbergeld et al. (1988) and Symansky and Hertz-Picciotto (1995) observed an increase of blood lead in nulliparous PosM women after comparing them with multiparous women. This finding suggests that pregnancy, and probably breast-feeding as well, may mobilize the lead deposited in bone simultaneously with calcium, to meet the calcium requirements observed in pregnancy and lactation, leaving smaller amounts of lead to be mobilized during the menopause transition. These results have not been confirmed by other investigators (Brown et al. 2000; Muldoon et al. 1994; Weyerman and Brenner 1998). In our study PosM women who breast-fed had higher bone lead levels (21.2 and 18.1 μg of lead per gram of bone mineral; $p = 0.23$). These results are similar to those reported by Brown et al. (2000) and probably reflect the fact that this cohort of women breast-fed during the years of high lead concentrations in the Mexico City air and thus incorporated additional lead during the bone gain phase that is known to follow pregnancy and lactation (Kalkwarf et al 1997).

HRT, alone or combined, prevents bone resorption and increases the BMD in trabecular and cortical bones of women with and without metabolic bone disease (Berlin et al. 1995; Gruber et al. 1997; Webber et al. 1995). This effect may lead to a decrease of lead mobilization from bone together with a reduction in blood lead levels. Webber et al. (1995) reported that women with HRT showed greater bone lead concentrations, especially in cortical bone, without having a simultaneous decrease in blood lead. In our study, 46.4% of the PosM women used HRT, and the blood lead levels observed among them were lower than those in nonusers (difference of 2.1 μg/dL; $p < 0.05$). In addition, we found that trabecular and cortical bone lead levels were higher in women who used HRT (1.19 and 0.43 μg Pb/g of bone mineral for patella and tibia, respectively). This observation supports the hypothesis that HRT reduces bone resorption, and by preventing lead mobilization from bone and diminishing blood lead levels, HRT may be considered a preventive measure in PosM women with high bone lead levels.

Compared with women of child-bearing age living in Mexico City (Brown et al. 2000) as well as perimenopausal women living in the United States (Korrick et al. 2002), the mean bone lead levels seen in these women were significantly higher. This finding reflects the fact that women participating in our study were living in Mexico City during the time that gasoline had a higher lead content and thus were subject to higher environmental lead exposures in the recent past. The adjusted regression coefficient of patella bone lead on blood lead predicted an increase of 0.80 μg blood lead/μg bone lead for women of child-bearing age and of 0.050 μg blood lead/μg bone lead for perimenopausal women, which were lower than estimated in this study (blood lead 0.135 μg/μg of bone lead).

Our study has potential limitations that may affect the inferences derived from these data. The participants were primarily low- and middle-class women who voluntarily attended an osteoporosis program and were not a random sample of the general population. Thus, our results cannot be generalized to all women living in Mexico City. Of note, we found differences, in terms of both blood lead levels and height, between women attending the screening program and women taking part in bone lead measurements. However, the differences observed in blood lead levels decreased once we adjusted for other variables such as use of ceramics, age, and menopausal status; therefore, it is unlikely that selection bias could explain our findings. We used simple questionnaire data to characterize environmental exposure to lead-glazed ceramic ware and thus may have underestimated the contribution to blood

Table 4. Results from multivariate linear regression of blood lead levels (log-e, microgram per deciliter) on selected predictors of study participants

Variable	Coefficient	*p*-Value	95% CI
Age linear (years)	–0.063	0.01	–0.113 to –0.013
Age squared (years^2)	0.0005	0.04	0.0001 to 0.001
Patella lead (μg Pb/g mineral bone)	0.012	< 0.01	0.008 to 0.015
Time postmenopausal (1–24 months)[a]	0.284	< 0.01	0.111 to 0.456
Time postmenopausal (≥ 25 months)[a]	0.204	0.03	0.020 to 0.388
Body mass index (kg/height in m)^2	0.015	0.03	0.001 to 0.029
Keeps food in lead-glazed ceramics	0.221	< 0.01	0.100 to 0.342
Education level (6–9 years)[b]	–0.191	0.040	–0.373 to –0.009
Education level (≥ 10 years)[b]	–0.296	< 0.01	–0.506 to –0.085
Time living in Mexico City (years)	0.007	< 0.01	0.003 to 0.012
Constant	3.41	< 0.01	2.03 to 4.784

[a]Years since menopause is in reference to PreM. [b]Educational level of 0–5 years is the reference category.

lead levels of this major known source of environmental lead exposure in Mexico. Only 16% of our study group (n = 36) were premenopausal, limiting our ability to conduct a more in-depth analysis of potential interactions such as the potential modifying effect of menopausal status on other factors that determined blood or bone lead levels. The cross-sectional nature of these data also limited our ability to do more sophisticated kinetic modeling of bone lead–blood lead interrelationships.

Suspicion exists that the accumulation of lead in bone itself represents a risk factor for osteoporosis. Individual cases such as the subjects reported by Berlin et al. (1995) who had occupational lead exposure, a bone fracture, and diagnosis of idiopathic osteoporosis provide some circumstantial evidence of such a relationship. Other evidence supporting the hypothesis that lead can directly damage bone includes observations of fetal and neonatal growth reduction and the development of osteopenia in experimental animals exposed to lead (Gruber et al. 1997). Pounds et al. (1991) reported that bone cells, both *in vitro* and *in vivo*, may be impaired by the presence of lead. However, additional studies are required to directly assess this hypothesis and to investigate indirect routes by which lead may be related to osteoporosis, such as the possibility that lead affects calcium absorption at the level of the digestive tract or that lead reduces circulating levels of 1,25-dehydrocholecalciferol, as has been noted in children by Mahaffey et al. (1982).

The increase in blood lead concentrations that result from bone resorption after menopause may, in turn, be associated with health effects that have not been adequately studied in elderly women. Studies of subjects in other age groups show that relatively modest exposures to lead are associated with neurologic dysfunction, behavioral disorders, hypertension, renal damage, and hematologic changes (Vig and Hu 2000). It may be particularly important to study the relationship between blood and bone lead levels and cognitive impairment in perimenopausal women because of the potential modifying role played by osteoporosis in these women.

References

Aro ACA, Todd AC, Amarasiriwardena C, Hu H. 1994. Improvement in the calibration of 103CD K x-ray fluorescence systems for measuring bone lead in vivo. Phys Med Biol 39:2263–2271.

Barry PSI, Mossmann DB. 1970. Lead concentration in human tissues. Br J Ind Med 27:339–351.

Berlin K, Gerhardsson L, Borjesson J, Lindh E, Lundstrom N, Schutz A, et al. 1995. Lead intoxication caused by skeletal disease. Scand J Work Environ Health 21:296–300.

Brown MJ, Hu H, Gonzalez-Cossio T, Peterson K, Sannin LH, Fishbein E, et al. 2000. Determinants of bone and blood lead levels in the early postpartum period. Occup Environ Med 57:535–541.

Cummings SR, Kelsey JL, Nevitt MC, et al. 1985. Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev 7:178–208.

Elders PJ, Netelenbos JC, Lips P, van Ginkel FC, van der Stelt PF. 1988. Accelerated vertebral bone loss in relation to the menopause: a cross-sectional study on lumbar bone density in 286 women of 46 to 55 years of age. Bone Miner 5:11–19.

Gruber H, Gonick H, Khalil-Manesh F, Sánchez T, Motsinger S, Meyer M, et al. 1997. Osteopenia induced by long-term, low-and-high-level exposure of the adult rat to lead. Miner Electrolyte Metab 23:65–73.

Gulson BL, Mahaffey KR, Mizon KJ, Korsch MJ, Cameron MA, Vimpani G. 1995. Contribution of tissue lead to blood lead in adult female subjects based on stable lead isotope methods. J Lab Clin Med 125:703–712.

Hernández-Avila M, González VC, Palazuelos E, Hu H, González VME, Rivera MD. 2000. Determinants of blood lead levels across the menopausal transition. Arch Environ Health. 55:355–362.

Hernández-Avila M, Romieu I. 1991. Lead glazed ceramics as major determinants of blood lead levels in Mexican women. Environ Health Perspect 94:117–120.

Hu H, Aro A, Roknitzky A. 1995. Bone lead measured by x-ray fluorescence: epidemiological methods and a new biomarker. Environ Health Perspect 103(suppl 1):105–110.

Hu H, Rabinowitz M, Smith D. 1998. Bone lead as a biologic marker in epidemiologic studies of chronic toxicity: conceptual paradigms. Environ Health Perspect 106:1–8.

Kalkwarf KJ, Specker BL, Bianchi DC, Ranz J, Ho M. 1997. The effect of calcium supplementation on bone density during lactation and after weaning. N Engl J Med 337:523–528.

Korrick SA, Schwartz J, Tsaih SW, Hunter DJ, Aro A, Rosner B, et al. 2002. Correlates of bone and blood lead levels among middle-aged and elderly women. Am J Epidemiol 156:335–343.

Kosnett MJ, Becker CE, Osterloh J, Kelly TJ, Pasta DJ. 1994. Factors influencing bone lead concentration in a suburban community assessed by noninvasive K Xray fluorescence. JAMA 271:197–203.

Lockitch G. 1993. Perspectives on lead toxicity. Clin Biochem 26:371–381.

Mahaffey KR, Rosen JF, Chesney RW, et al. 1982. Associations between age, blood lead, and serum 1,25-dihydroxycholecalciferol levels in children. Am J Clin Nutr 35:1327–1331.

Muldoon SB, Cauley JA, Kuller LH, Scott J, Rohay J. 1994. Lifestyle and socidemographic factors as determinants of blood lead levels in elderly women. Am J Epidemiol 139:599–608.

Nilas L, Christiansen C. 1988. Rates of bone loss in normal women: evidence of accelerated trabecular bone loss after menopause. Eur J Clin Invest 18:529–534.

Pounds GJ, Long GJ, Rosen JF. 1991. Cellular and molecular toxicity of lead in bone. Environ Health Perspect 91:17–32.

Riggs BL, Melton LJ III. 1986. Involutional osteoporosis. N Engl J Med 314(26):1676–1986.

Romieu I, Palazuelos E, Hernández-Avila M, et al. 1994. Sources of lead exposure in Mexico City. Environ Health Perspect 102:384–389.

Ruegsegger P, Dambacher MA, Ruegsegger E, Fischer JA, Anliker M. 1984. Bone loss in premenopausal women. A cross-sectional and longitudinal study using quantitative computed tomography. J Bone Surg 66:1015–1023.

Silbergeld EK, Sauk J, Somerman M, Todd A, McNeill F, Fowler B, et al. 1993. Lead in bone: storage site, exposure source, and target organ. Neurotoxicology 14:225–236.

Silbergeld EK, Schwartz J, Mahaffey K. 1988. Lead and osteoporosis: mobilization of lead from bone in postmenopausal women. Environ Res 47:79–94.

Symansky E, Hertz-Picciotto I. 1995. Blood lead levels in relation to menopause, smoking and pregnancy history. Am J Epidemiol 141:1047–1058.

Vig EK, Hu H. 2000 Lead toxicity in older adults. J Am Geriatr Soc 48(11):1501–1506.

Webber CE, Chette DR, Bowins RJ, Beaumont LF, Gordon CL, Song X, et al. 1995. Hormone replacement therapy may reduce the return of endogenous lead from bone to the circulation. Environ Health Perspect 103:1150–1153.

Weyerman M, Brenner H. 1998. Factors affecting bone demineralization and blood lead levels of postmenopausal women. A population-based study from Germany. Environ Res 76:19–25.

WHO. 1994. Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis. Technical Report Series. Geneva:World Health Organization.