Influence of Bone Resorption on the Mobilization of Lead from Bone among Middle-aged and Elderly Men: The Normative Aging Study

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Bone stores of lead accrued from environmental exposures and found in most of the general population have recently been linked to the development of hypertension, cognitive decrements, and adverse reproductive outcomes. The skeleton is the major endogenous source of lead in circulating blood, particularly under conditions of accelerated bone turnover and mineral loss, such as during pregnancy and in postmenopausal osteoporosis. We studied the influence of bone resorption rate on the release of lead from bone in 333 men, predominantly white, middle-aged and elderly (mostly retired) from the Boston area. We evaluated bone resorption by measuring cross-linked N-telopeptides of type I collagen (NTx) in 24-hr urine samples with an enzyme-linked immunosorbent assay. We used K-X-ray fluorescence to measure lead content in cortical (tibia) and trabecular (patella) bone; we used graphite furnace atomic absorption spectroscopy and inductively coupled plasma mass spectroscopy to measure lead in blood and urine, respectively. After adjustment for age and creatinine clearance, the positive relation of patella lead to urinary lead was stronger among subjects in the upper two NTx tertiles (β for patella lead ≥ 0.15) than in the lowest NTx tertile (β for patella lead = 0.008; overall p-value for interactions = 0.06). In contrast, we found no statistically significant influence of NTx tertile on the relationship of blood lead to urinary lead. As expected, the magnitude of the relationship of bone lead to urinary lead diminished after adjustment for blood lead. Nevertheless, the pattern of the relationships of bone lead to urinary lead across NTx tertiles remained unchanged. Furthermore, after adjustment for age, the relation of patella lead to blood lead was significantly stronger in the upper two NTx tertiles (β for patella lead ≥ 0.125) than in the lowest NTx tertile (β for patella lead = 0.072). The results provide evidence that bone resorption influences the release of bone lead stores (particularly patella lead) into the circulation. Key words: bone, bone, environmental exposure, K-X-ray fluorescence, lead, N-telopeptides, urine. Environ Health Perspect 109:995–999 (2001). [Online] http://ehpnet1.niehs.nih.gov/docs/2001/109p995-999tsaih/abstract.html

Although environmental exposure to lead in the United States has been reduced substantially since the 1970s (1), bone stores of lead accrued from environmental exposures and found in most of the general population have recently been linked to the development of hypertension (2,3), cognitive decrements (4,5), and adverse reproductive outcomes (6). In adults, about 95% of the total body burden of lead is stored in the skeleton (7). Lead enters bone at the time of mineral deposition and leaves bone at the time of bone resorption. Therefore, factors affecting bone turnover, such as pregnancy (8–10), lactation (9), and menopause and osteoporosis (11), can be expected to be associated with increased mobilization of lead from the skeleton.

Cross-sectional studies have shown that bone lead concentration increases with age (12,13). However, in longitudinal analyses of 70 participants in the Normative Aging Study (NAS) (14), bone lead levels (particularly those in the patella, a trabecular bone) decreased over a 3-year follow-up interval. This finding is not surprising in light of recent declines in population blood lead levels (1). Given that an increase in bone resorption is a characteristic of aging in both men and women, resorptive losses may also contribute to longitudinal declines in bone lead, particularly in older populations. Aging-associated release of bone lead into the circulation is, in fact, a potentially important source of soft-tissue lead exposure and toxicity (11). Indeed, in U.S. population surveys, older adults have among the highest blood lead levels, second only to the peak observed in young children (1).

Plasma lead measurement provides critical information on the bioavailable fraction of whole-blood lead (15–17) but is difficult to perform accurately because levels are extremely low and may be affected by contamination from hemolysis, sampling, and laboratory handling (18–20). An alternative is the measurement of urinary lead, which originates from plasma lead filtered at the glomerular level; thus, urinary lead levels adjusted for glomerular filtration rate serve as a marker of plasma lead.

To assess the influence of bone resorption on bone mobilization from bone, particularly in studies in which bone lead levels are being assessed as potential predictors of toxicity, biochemical markers that provide an index of increased bone resorption are needed. Urine cross-linked N-telopeptides of type I collagen (NTx) are derived specifically from bone collagen degradation and are considered a sensitive and specific marker of bone resorption (21–23). In this study, we assessed the influence of bone resorption (estimated by 24-hr urinary NTx) on the relationships of bone lead and blood lead with urinary lead in a group of 333 middle-aged and elderly men. The independent contribution of bone lead to urinary lead has been reported previously (24).

Materials and Methods

Study population. This investigation took advantage of an ongoing longitudinal cohort study of aging, the NAS, established in 1961 (25). The study cohort initially consisted of...
2,280 predominantly white men from the Greater Boston, Massachusetts, area. The men were 21–80 years of age upon enrollment. All participants were free of known chronic medical conditions at the time of enrollment; participants were excluded if they had any history of hypertension, cancer, recurrent asthma, sinusitis, bronchitis, diabetes, gout, or peptic ulcer. Since their enrollment in 1961–1968, participants have been reevaluated at 3- to 5-year intervals by a detailed core examination including collection of medical history information, routine physical examinations, laboratory tests, and questionnaires. Dietary intake has been assessed with a self-administered, semiquantitative food-frequency questionnaire adapted from a well-validated questionnaire used elsewhere (26).

Beginning in 1987, a 24-hr urine specimen was obtained at each subject’s regularly scheduled examination. In addition, a blood sample for lead analysis was collected at each visit since 1988. Beginning in 1991, NAS participants were recruited for a substudy of K-X-ray fluorescence (KXRF) bone lead measurement. For the present study, we identified 380 NAS participants who were subjects in the KXRF bone lead substudy and who had 24-hr urine specimens collected at two consecutive visits that were judged to be valid (i.e., had a volume of 750–2,900 mL and a collection time of 20–28 hr). We retrieved frozen urine aliquots from the first 24-hr urine specimen, which coincided with the participant’s initial (baseline) bone lead determination and in which lead had previously been measured; thawed these aliquots and measured their NTx content; and examined bone resorption as a potential modifier of the relationships of bone lead and blood lead to blood lead.

All research performed in our study was approved by the Human Research Committees of Brigham and Women’s Hospital and the Department of Veterans Affairs Outpatient Clinic in Boston.

**Blood lead.** We obtained and analyzed whole-blood samples for lead by graphite furnace atomic absorption with Zeeman background correction (ESA Laboratories, Chelmsford, MA). Values below the minimum detection limit of 1 µg/dL (n = 3, < 1%) were coded as 0. The instrument was calibrated with National Institute of Standards and Technology Standard Reference Material (NIST SRM 955a, lead in blood) after every 20 samples. Ten percent of samples were run in duplicates; at least 10% of the samples were controls and 10% were blanks. In tests on reference samples from the Centers for Disease Control and Prevention (Atlanta, GA), the coefficient of variation (CV) ranged from 8% for concentrations from 10 to 30 µg/dL to 1% for higher concentrations. In this study, the CV was 5% for concentrations below 10 µg/dL. Compared with a NIST target of 5.7 µg/dL, 24 measurements by this method gave a mean [standard deviation (SD)] of 5.3 (1.2) µg/dL.

**Bone lead.** We measured bone lead in each subject’s mid-tibia shaft and patella with a KXRF instrument (ABIOMED, Inc., Danvers, MA). The tibia and patella have been targeted for bone lead research because they consist mainly of cortical and trabecular bone, respectively. A technical description and the validity specifications of the KXRF instrument have been published elsewhere (27,28). The instrument provides an unbiased estimate of bone lead levels (normalized for bone mineral content and expressed as micrograms of lead per gram of bone mineral) and an estimate of the uncertainty associated with each measurement.

**Urinary lead.** The methods used for urinary lead measurement in this study are described in detail elsewhere (24). In brief, collection of 24-hr urine began after the first void of the morning and continued through the first void of the subsequent morning. Urine samples were collected in the presence of an antioxidant (sodium metabisulfite) and 6 M hydrochloric acid to achieve a pH between 2 and 3. The samples were stored at −20°C until assay; thawed, aliquoted, and frozen until assay; and then dried at room temperature before analysis.

**Creatinine.** We used the Beckman Creatinine Analyzer 2 (Beckman, Brea, CA) to measure creatinine in serum and in archived (frozen) 24-hr urine samples by routine laboratory method (Jaffe method). This method of analysis has intra-assay CVs of 1.3% at 1.2 mg/dL for serum and 2.4% at 17.7 mg/dL for urine, respectively, and interassay CVs of 3.3% at 1.1 mg/dL for serum and 3.1% at 17.6 mg/dL for urine, respectively.

**Statistical methods.** To account for interindividual variability of glomerular filtration rate, we used the Beckman Creatinine Analyzer 2 to determine creatinine clearance rate (mL/min).

### Table 1. Characteristics of 333 middle-aged and elderly male participants in a study of the influence of bone resorption on bone lead mobilization.

| Variables                        | Total (N = 333) | Low: < 34 (n = 115) | Medium: 34–< 52 (n = 116) | High: ≥ 52 (n = 112) | p-Value (ANOVA) |
|----------------------------------|-----------------|---------------------|---------------------------|----------------------|-----------------|
| Age (years)                      | 66.4 (6.3)      | 65.5 (3.7)          | 67.0 (6.08)               | 66.7 (6.7)           | NS              |
| Body mass index (kg/m²)          | 27.7 (3.7)      | 28.5 (3.7)          | 27.7 (3.4)                | 27.0 (3.8)           | 0.01            |
| Urinary lead (µg/day)            | 5.7 (3.3)       | 5.3 (3.3)           | 5.5 (3.1)                 | 6.0 (3.6)            | NS              |
| Blood lead (µg/dL)               | 6.1 (4.0)       | 5.8 (3.7)           | 5.9 (3.7)                 | 6.6 (4.6)            | NS              |
| NTx (nM BCE/mM creatinine)       | 31.1 (17.3)     | 31.0 (17.2)         | 32.8 (17.8)               | 29.7 (17.0)          | NS              |
| Urinary creatinine (mg/mL)       | 21.3 (12.2)     | 20.6 (11.4)         | 22.1 (12.0)               | 21.4 (13.2)          | NS              |
| Serum creatinine (mg/dL)         | 1.2 (0.2)       | 1.2 (0.2)           | 1.2 (0.2)                 | 1.2 (0.1)            | NS              |
| NTx range (nM BCE/mM creatinine) | 80.9 (41.4)     | 94.8 (41.4)         | 98.6 (42.7)               | 99.2 (40.7)          | NS              |
| NTx distribution (SD)            | 87.5 (29.3)     | 93.6 (33.6)         | 94.9 (27.6)               | 79.6 (21.0)**        | 0.01            |
| Urinary NTx (nM BCE)             | 417.8 (324.1)   | 219.4 (106.0)       | 354.1 (165.7)**           | 681.8 (402.2)**      | < 0.01          |
| Urinary NTx (nM BCE/mM creatinine)| 48.9 (33.8)    | 26.2 (5.5)          | 41.2 (4.9)**              | 79.5 (42.7)**        | < 0.01          |

Abbreviations: BCE, bone collagen equivalent (equivalent moles of bone type I collagen from which the antigen is derived); NS, not significant (p > 0.05).

*Three subjects (€ 1%) who had blood lead under detection limit of 1 µg/dL were coded as “0.” *Statistically significantly different from low NTx tertile. **Statistically significantly different from medium NTx tertile.
function, we adjusted urinary lead levels for creatinine clearance rate (CCr), an estimate of glomerular flow rate calculated from the clearance rate of endogenously produced creatinine. We calculated CCr (millimeters per minute) as total amount of urine creatinine over 24 hr: milligrams/serum creatinine. We also included vitamin C intake (30,31) and calcium intake (32) in all regression models. All nutrients examined were adjusted for total energy intake to minimize extraneous error (caused by individual differences in total food intake) in estimating specific nutrient intake and to reduce potential confounding by total food intake. We applied a regression diagnostics procedure to the final model to identify potential outliers and influential points. All analyses were performed using SAS version 6.12 (SAS Institute, Cary, NC).

Results
Among 380 eligible subjects, 26 with missing data on blood lead, patella lead, urinary lead, CCr, or NTx, and 19 subjects with reduced renal function (serum creatinine concentrations of > 1.5 mg/dL) were excluded. Two subjects were identified as outliers by regression diagnostics because of their low urinary lead levels (< 0.47 µg/day; population mean ± SD was 5.7 ± 3.3 µg/day) and moderate to high blood lead levels (≥ 14 µg/dL; population mean ± SD was 6.1 ± 4.0 µg/dL) and bone lead levels (patella lead levels ≥ 46 µg/g; population mean ± SD was 31.1 ± 17.3 µg/g) and moderate to high NTx levels (NTx = 50 and 193 nMBCE/mM creatinine; population mean ± SD was 48.9 ± 33.8 nMBCE/mM creatinine). Thus, 47 subjects were excluded from this analysis. Most (97%) of the remaining 333 subjects were white, and their characteristics are summarized in Table 1.

The mean of NTx in this group of middle-aged and elderly men was 48.9 nMBCE/mM creatinine (Table 1). There was no significant difference in blood, bone, or urinary lead levels across tertiles of NTx by ANOVA. As expected, lead measures in blood and bone were moderately correlated with CCr adjusted urinary lead (r = 0.3–0.6, all p < 0.01; Table 2). NTx was marginally associated with adjusted urinary lead (r = 0.10, p = 0.07).

Patella lead and tibia lead had stronger associations with urinary lead in the upper two NTx tertiles than in the lowest NTx tertile (Tables 3 and 4). For example, after adjusting for age and creatinine clearance, the relation of patella lead to urinary lead was approximately two times greater in the medium and high NTx tertiles (β = 0.017 and 0.015) than in the low NTx tertile (β = 0.008; Table 4). We observed similar results with regard to the relation of tibia lead to urinary lead. However, we observed a potentially significant modifying effect of NTx only on the relationship between patella lead and urinary lead (Table 3; overall p-value for interactions = 0.06). We found no statistically significant influence of NTx on the relationship of bone lead to urinary lead.

As expected, the magnitude of the relationship of bone lead to urinary lead diminished after adjustment for blood lead (Table 4). Nevertheless, the pattern of the relationships of patella lead and tibia lead to urinary lead across NTx tertiles remained unchanged. Furthermore, the relation of patella lead to urinary lead was approximately three times greater in the medium and high NTx tertiles (β = 0.010 and 0.009) than in low NTx tertile (β = 0.003). None of the other variables (body mass index, alcohol consumption, cumulative cigarette smoking, dietary intake of vitamin C and calcium) predicted urinary lead level, nor did the inclusion of these variables in the models change the regression coefficients of bone or blood lead levels to a notable extent.

### Table 2. Pearson correlation of biologic markers of lead dose with age and urinary N-telopeptide (n = 333).

| Variables          | Pearson correlation (n = 333) | β (SE) |
|--------------------|-----------------------------|--------|
| log(e(N-telopeptide)) | 0.07             | 0.01   |
| log(e(urinary lead))  | 0.04             | 0.04   |
| Patella lead (µg/g)  | 0.31**            | 0.39*  |
| Tibia lead (µg/g)   | 0.35*             | 0.27*  |

### Table 3. Multiple regression analysis of 24-hr urinary lead levels on blood or bone lead and adjusted for age, urinary N-telopeptide tertiles, and the interaction between each lead measure and NTx tertile (n = 333).

| Independent variables | β (SE) |
|-----------------------|--------|
| Age (years)           | 0.00   |
| Blood lead (µg/dL)    | 0.071 (0.011)** | 0.008 (0.003)** |
| Patella lead (µg/g)   | 0.31** | 0.39*  |
| Tibia lead (µg/g)     | 0.35*  | 0.27*  |

### Notes
- 24-hr urinary lead was log(e) transformed and adjusted for creatinine clearance.
- *p ≤ 0.05; **p ≤ 0.01.
using standard metabolic methods (35–37) and in those using KXRF (12,38–40). Furthermore, a recent study reported that bone lead (particularly patella lead) exerts an additional independent influence on plasma lead after adjusting for whole blood lead in individuals with no history of occupational lead exposure (41). Our findings support the argument that lead in trabecular bone is more available for mobilization and has more influence on the amount of lead excreted in urine than cortical bone.

Bone loss occurs with aging in both men and women at a reported rate of 5–10% per decade (42). Data on NTx in middle-aged and elderly men are limited. Although data on 24-hr NTx excretion are likewise sparse, NTx levels in a previous study where 24-hr values were available (43) were substantially lower in men (\(n = 57\), mean ± SD = 30.5 ± 20.4 nM BCE/mM creatinine) than in postmenopausal women (\(n = 69\), mean ± SD = 43.3 ± 27.7 nM BCE/mM creatinine). A similar gender difference was reported in a study where NTx was measured in morning urine from the elderly (\(n = 374\), mean = 30.0 nM BCE/mM creatinine for men; \(n = 364\), mean = 45.7 nM BCE/mM creatinine for postmenopausal women not using estrogen) (44). Although the current study was restricted to male participants (\(n = 333\), mean ± SD = 48.9 ± 33.8 nM BCE/mM creatinine), given similar or greater bone resorption among postmenopausal women, our results support a potentially important role of bone resorption as a modifier of lead distribution and its resultant toxicity in both men and women.

Our study was limited by its cross-sectional nature, which made it impossible to

### Discussion

To the best of our knowledge, this is the first study to assess the influence of bone resorption on the release of lead from bone using a biomarker of bone resorption. We observed a positive relation of blood lead and bone lead to urinary lead after adjustment for CCr. As reported previously, although blood lead was a consistently important determinant of urinary lead in the study population, bone lead was shown to contribute independently to urinary lead (24). Moreover, the current analysis expands on this previous observation by suggesting that the independent contribution of bone lead to urinary lead was higher among subjects with greater bone resorption, although the association was significant for patella but not for tibia lead measures (Table 4). Some kinetic models as well as empirical observations have suggested the possibility of an independent contribution of bone lead to plasma lead (33,34). Bone lead was a better biomarker of lead dose than blood lead in recent studies of the relationship of low-level lead exposure to hypertension in men (2) and in women (3), cognitive decrements (4,5), and low birth weight (6). These findings raise concerns that blood lead levels not only inadequately represent levels of lead accumulated in bone but also inadequately represent levels of lead in plasma (the primary source of bioavailable lead to most body organs), because bone lead stores may influence plasma lead levels independently of blood lead. Our findings support these concerns.

The most likely explanation for our failure to find a significant modifying effect of NTx on the trabecular lead—urinary lead or tibia lead—blood lead relationships is that as cortical bone, the tibia is less prone to bone turnover than the patella, which is trabecular bone. Trabecular bone has greater metabolic activity than cortical bone. Accordingly, lead stored in trabecular bone has shown a stronger association with circulating lead both in studies

### Table 4. Multiple regression analysis of 24-hr urine lead levels on bone lead and blood lead by urinary N-telopeptide (NTx) tertiles (\(n = 333\)).

| Model | Low: \(< 34\) (\(n = 115\)) | Medium: \(34 – < 52\) (\(n = 106\)) | High: \(\geq 52\) (\(n = 112\)) |
|-------|-----------------------------|---------------------------------|-------------------------------|
| Age   | \(-0.009\) (0.006)           | \(-0.016^*\) (0.007)           | \(-0.010\) (0.008)           |
| Patella lead | \(0.008^*\) (0.003) | \(0.017^*\) (0.002) | \(0.015^*\) (0.003) |
| Blood lead | --- | --- | --- |
| Age   | \(-0.004\) (0.006)           | \(-0.010\) (0.006)           | \(-0.009\) (0.007)           |
| Patella lead | \(0.003\) (0.002) | \(0.010^*\) (0.003) | \(0.009^*\) (0.003) |
| Blood lead | \(0.073^*\) (0.011) | \(0.058^*\) (0.011) | \(0.041^*\) (0.011) |
| Age   | \(-0.007\) (0.008)           | \(-0.010\) (0.007)           | \(-0.014\) (0.008)           |
| Tibia lead | \(0.010^*\) (0.004) | \(0.019^*\) (0.004) | \(0.017^*\) (0.004) |
| Blood lead | --- | --- | --- |
| Age   | \(-0.002\) (0.006)           | \(-0.005\) (0.006)           | \(-0.012\) (0.008)           |
| Tibia lead | \(0.001\) (0.004) | \(0.009^*\) (0.003) | \(0.011^*\) (0.004) |
| Blood lead | \(0.076^*\) (0.011) | \(0.072^*\) (0.011) | \(0.047^*\) (0.011) |

Values shown are regression coefficients (\(\beta\)) and SEs (in parentheses). *24-hr urinary lead was loge transformed and adjusted for creatinine clearance. \(p < 0.05; \) **\(p < 0.01.\)

### Table 5. Multiple regression analysis of blood lead on age and bone lead by urinary N-telopeptide (NTx) tertiles (\(n = 333\)).

| Model | Low: \(< 34\) (\(n = 115\)) | Medium: \(34 – < 52\) (\(n = 106\)) | High: \(\geq 52\) (\(n = 112\)) |
|-------|-----------------------------|---------------------------------|-------------------------------|
| Age   | \(-0.069\) (0.055)           | \(-0.113\) (0.052*\)           | \(-0.038\) (0.062)           |
| Patella lead | \(0.072\) (0.020) | \(0.130\) (0.018)** | \(0.125\) (0.024)** |
| Age   | \(-0.070\) (0.054)           | \(-0.063\) (0.057)           | \(-0.044\) (0.070)           |

Values shown are regression coefficients (\(\beta\)) and SEs (in parentheses). \(p < 0.05; \) **\(p < 0.01.\)
delineate temporal relationships among factors. Renal function may influence the excretion of NTx and lead because both are excreted through glomerular filtration. To minimize the effect of renal function, we excluded all subjects with renal impairment (serum creatinine levels > 1.5 mg/dL) and adjusted urinary lead for creatinine clearance, an estimate of glomerular filtration function. Furthermore, we repeated the analyses with new NTx tertiles defined by NTx values before creatinine correction, and the stratified regression results were similar to those reported in Tables 4 and 5, but the interaction between patella lead and NTx (Table 3) was no longer significant. Thus, it is unlikely that our findings were significantly influenced by variability in renal function.

Lead in diet, in addition to bone lead and blood lead, may contribute substantially to lead in urine for individuals without occupational exposure. Our study was further limited by the fact that we did not measure dietary intake of lead and were unable to distinguish between lead from the skeleton and lead from dietary sources. Nevertheless, in an aging population such as the NAS, with moderate to high bone lead levels, the relative contribution of recent diet to urinary lead excretion is likely to be minimal.

In summary, our findings are consistent with the hypotheses that bone resorption modifies the release of lead from bone; that bone, independent of blood, is a source of lead in plasma among middle-aged and elderly men because lead excreted in urine is presumed to be derived from plasma; and that whole-blood lead levels do not directly predict plasma lead levels. Our findings also indicate that urinary NTx levels can be used in epidemiologic studies to measure the potential modifying influence of bone resorption on the risk of toxicity as assessed by KXRF-measured bone lead levels.

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