Bone Lead as a New Biologic Marker of Lead Dose: Recent Findings and Implications for Public Health

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Measurements of lead in bone have recently become the focus of research because a) bone lead levels serve as a cumulative dosimeter of lead exposure over many years (because of lead's long residence time in bone), and cumulative exposure may be more predictive of chronic toxicity than recent exposure, which is what blood lead levels mostly reflect; b) there is suspicion that heightened bone turnover (e.g., during pregnancy, lactation, and aging) may liberate enough stored lead to pose a significant threat of delayed toxicity; and c) although lead exposure has largely declined in the United States over the past 10 to 15 years, decades of heavy environmental pollution have resulted in significant accumulation of lead in bone among most members of the general U.S. population. Epidemiologic research on the impact of lead stored in bone is now possible with the development of $^{199m}$Cd K-X-ray fluorescence (KXRF) instruments for the in vivo measurement of lead in bone. In this paper, the KXRF method will be briefly reviewed, followed by a summary of several Superfund-supported studies (and others) of blood lead and KXRF-measured bone lead in which these measures are compared as biologic markers of lead dose. Measurement of bone lead in epidemiologic studies has proved useful in exposure assessment studies, i.e., in identifying factors that contribute most to retained body lead burden, and in investigating cumulative lead exposure as a risk factor for poor health outcomes such as hypertension, kidney impairment, cognitive impairment, behavioral disturbances, and adverse reproductive outcomes.

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Introduction

Monitoring and control of exposure to lead in the workplace, home, and community has benefited tremendously from measuring levels of lead in blood, a technique that has been widely performed in laboratories for this purpose for approximately 3 decades. Although early laboratory methods suffered from problems with standardization, precision, and the challenge of controlling the ever-present threat of external contamination, the advent of anodic stripping voltammetry, atomic absorption spectroscopy, clean laboratory techniques, and external reference standards has greatly improved the reliability and accuracy of blood lead measurements. Such measurements are now being widely performed in laboratories throughout the world and form the basis for the U.S. Centers for Disease Control and Prevention recommendations on the biologic monitoring of children (1) and the U.S. Occupational Safety and Health Administration's recommendations on the biologic monitoring of workers (2).

Blood lead levels, however, may not be an adequate reflection of an individual's full risk for lead-associated toxicity. This concern is based on several realizations: Lead accumulates in skeletal bone over time, comprising 90 to 95% of lead burden in adults and 80 to 95% in children; (3,4) cumulative lead exposure may be more predictive of some forms of chronic toxicity than current lead exposure (5); and although blood lead levels are generally well correlated with current lead exposure, they are poorly indicative of lead accumulated in bone (6). Blood lead levels remain constant when exposures are steady-state while bone lead levels continue to rise, and blood lead levels decline once exposure ceases in the presence of persistently elevated bone lead levels. Thus, following cessation of exposure among chronically exposed adults, blood lead levels have a median biologic half-life of about 1 month (range 7–63 days) (7,8), and therefore mostly reflect recent lead exposure, whereas bone lead levels, with a half-life of years to decades, reflect accumulated exposure.

Finally, the growing appreciation of bone as a dynamic organ throughout life has heightened concern that lead stored in bone can be mobilized into circulation, providing a mechanism for delayed toxicity. This phenomenon has been suggested by a number of recent studies of physiologic states known to be accompanied by elevated bone turnover, such as the rapid growth of childhood (9), pregnancy (10,11), lactation, and osteoporosis (12,13), as well as a recent study of the impact of hormone replacement therapy on bone lead mobilization (14).

Measuring Lead in Bone: K-X-Ray Fluorescence

Until recently, epidemiologic research on the implications of lead in bone has been hampered by the lack of a suitable noninvasive and convenient method for estimating an individual's cumulative lead dose. Shed primary teeth have been a reliable measure of lead dose to mineralized tissue, but this measure is suitable only for children and only at certain ages, severely limiting its application (15). The calcium disodium edetate (EDTA) mobilization test requires parental administration of the drug EDTA, collection of urine for hours to days, and monitoring for drug toxicity. In addition, the mobilizable fraction of lead measured by this test probably differs from bone lead levels, particularly among individuals whose main lead exposure was years ago or who have undergone chelation (16,17).

X-ray fluorescence (XRF) instruments, which make in vivo measurements of lead levels in bone, are quite promising in this regard (18,19). Two types of XRF instruments exist—L-X-ray fluorescence (LXRF) and K-X-ray fluorescence (KXRF). This paper focuses on KXRF, which has been the most widely used and validated
technology. Discussion and critiques of LXRF may be found elsewhere (20,21).

Most KXRF instruments use low-intensity gamma radiation, emitted by a $^{109}$Cd or $^{57}$Co γ-ray source, to provoke the emission of fluorescent photons from the target area of a test subject's anatomy. With specialized equipment, designs, statistical methods, and software, methods have been developed to count these photons and derive estimates of bone lead (in units of microgram Pb/gram bone mineral) with ever-improving precision and accuracy (22–24).

Our laboratory began a KXRF program by working with a commercial company (Abiomed, Inc., Danvers, MA) to develop a $^{109}$Cd instrument that uses a 200-mCi source in a 164° backscatter geometry (source-detector configuration) and is self-energy calibrating, automated, able to produce real-time results, usable on any site on either lower limb, and operable by a technician (25). For our next generation of instruments, we built our own instruments and switched to a 30-mCi $^{109}$Cd spot-source design and 180° backscatter geometry described first by Gordon et al. (23), and then by us (24), while preserving most of the ease-of-use features of the Abiomed instrument. In summary, a $^{109}$Cd 1.11 GBq (gigabecquerels) source of activity is sealed in a stainless steel capsule housed in a tungsten-alloy source holder. The $^{109}$Cd source is positioned coaxial with and at the center of the intrinsic Ge detector. The preamplifier signal is passed to an amplifier and the analog signal is converted into a digital signal with a fast analog-to-digital converter and then passed to a PC-based multichannel analyzer board (Figure 1).

A sample spectrum is displayed in Figure 2. The net lead signal is determined after subtraction of Compton background counts, using a nonlinear least-squares fit program first adopted and used by Chettle et al. (22). The lead fluorescence signal is then normalized to the elastic or coherently scattered X-ray signal, which arises predominantly from calcium present in bone mineral. The unit of measurement so derived is micrograms of lead per gram of bone mineral. The instrument also provides an estimate of uncertainty associated with each measurement. The uncertainty element is derived from a goodness-of-fit calculation and counting statistics of the spectrum curves. This value is equivalent to a single standard deviation if repeated measurements were taken. Thus, a typical measurement of tibia bone lead might be $17 \pm 3 \mu g/g$. The measurement uncertainty estimate allows a more rigorous interpretation of each measurement and can be used to weigh each measurement as compared to other measurements in the course of data analysis.

By normalizing the measurement to calcium counts, the measurement is rendered insensitive to variations in bone shape, size, density, histomorphometry, overlying tissue thickness, and a small amount of movement (26). Validation studies with repeated measurements have indicated the instrument provides a high degree of precision and accuracy of the point and measurement uncertainty estimates as compared to chemical analyses of lead-doped phantoms (24). Radiation dosimetry studies measuring dose to skin, bone red marrow, and the pelvic area have demonstrated that a typical $^{109}$Cd KXRF measurement gives extremely low effective dose values of less than 0.1 μSv (27).

![Diagram of K-X-ray fluorescence instrument: signal processing.](image)

Figure 1. K-X-ray fluorescence instrument: signal processing.

![Graphs A and B showing K-X-ray fluorescence spectra.](image)

Figure 2. Sample spectrum of Harvard K-X-ray fluorescence. (A) Lead concentration 50 μg/g. Lead peaks are mainly at the alpha-1 and beta-1,3 areas. (B) Detail of the alpha-1 peak.
significantly below a proposed limit of negligibility of 10 μSv (28).

The utility of KXRF-measured bone lead in serving as a biologic marker is critically dependent on several concepts that are common to all biologic markers and laboratory measurements. Much additional work, for example, has been done on calibration procedures using lead-doped phantoms (24), and documentation of precision and accuracy not only in phantoms, but also in cadaveric specimens with verification by atomic absorption spectroscopy or inductively coupled plasma mass spectrometry (26,29). In our laboratory, for example, we found that the correlation of measurements of eight targeted cadaveric tibias using our prototype KXRF instrument in relation to atomic absorption spectroscopy measurements of the same sites was 0.98 with an x intercept of −0.1 μg Pb/g bone mineral over cadaveric bone lead concentrations ranging from 16 to 120 μg/g (29). Gordon et al. (30) and Armstrong et al. (31) demonstrated good reproducibility of repeated KXRF measurements in low- and high-lead-exposed adults, respectively.

Studies of intraskeletal variability of lead concentration have also been performed, thus verifying that bone lead concentrations vary significantly from site to site, but in a consistent fashion (32,33). Thus, single-site bone lead measurements are fairly representative of total skeletal burden. An important exception is that the behavior of lead in bone seems to diverge along the lines of the two main architectural bone types—cortical bone and trabecular bone. This probably stems from the differing bone surface areas and bone turnover rates of these two bone types. As a consequence, some of the research groups in this area have chosen to make KXRF measurements at two separate sites (one chiefly cortical and one chiefly trabecular) for each individual. Chettle and colleagues (22,34) have tended to use the midtibia shaft and calcaneus as the cortical and trabecular bone sites, respectively, whereas we have chosen the midtibia shaft and the patella, respectively. We recently reported on the difference between the tibia and patella's rates of KXRF-measured bone lead decline over 3 years of repeated observations among middle-aged to elderly men from the general population (35). We found that over this time interval the geometric mean lead levels in the patella declined by 23% (95% confidence interval 14–31%), whereas the geometric mean lead levels in the tibia did not decline at all.

An important caveat related to KXRF measurements is that their precision is partially dependent on the mass of bone that is being measured. Thus, the thin bones of children are measured with larger error than the well-mineralized bones of adults. Most studies have also indicated that children tend to have lower bone lead levels in general [e.g., Wittmers et al. (32)]. Thus, the combination of lower bone lead levels and larger measurement error renders KXRF bone lead research in children quite difficult.

**Studies Using KXRF: Exposure–Dose Relationships**

By providing a biologic marker of cumulative dose, KXRF-measured bone lead can be used in epidemiologic studies that explore exposure–dose relationships and provide information on those factors that contribute most heavily to accumulated lead burden, particularly in studies of populations in which lead exposure is occurring through multiple possible pathways (as opposed to studies of industrially exposed workers in which the industrial lead exposure predominates). A summary of relevant studies is provided in Table 1. In an early study using KXRF measurements of finger bone lead, Price et al. (36) found that risk factors for elevated bone lead were childhood residence in a painted wooden house (probably exposure to lead paint) and various occupational exposures. Similarly, we found that growing up in older housing (which probably reflects exposure to lead paint) was a significant predictor of elevated tibia bone lead level among young to middle-aged adults (29). Kosnett et al. (37) found that total pack-years of cigarette smoking and, among women, a history of not having breast-fed an infant predicted higher tibia bone lead levels. In construction workers who performed a variety of activities with possible lead exposure, we found welding/brazing, paint stripping, carpet-laying, and exercise to be factors associated with elevated bone lead (38).

In Superfund-supported research, we studied a large group of community-exposed middle-aged to elderly men living in the metropolitan Boston, Massachusetts, area, none of whom had held any jobs associated with primary lead exposure (39). In analyses that considered age, race, education, retirement status, measures of both current and cumulative smoking, and alcohol consumption, the factors that remained significantly related to higher levels of bone lead were higher age, measures of cumulative smoking, and lower levels of education (39). Smoking entails lead exposure by a direct contribution from tobacco (which is contaminated by atmospheric lead deposition and lead arsenate pesticides) (40,41), increased hand-to-mouth activity, and possibly the enhanced permeability of a smoke-exposed respiratory tract (42). Education may be serving as a proxy for unmeasured cumulative environmental exposures such as home exposure to lead in dust and drinking water, home proximity to vehicular traffic, and/or occupational lead exposures.

The age-associated increases in bone lead among nonoccupationally exposed populations found in this study of Boston area middle-aged to elderly men (39), and in KXRF studies of Boston-area adolescents (43), Boston-area young adults (29), Boston-area women (44), Pennsylvania residents (37), adults in Swansea, Wales (45), and adults in southern Ontario,

### Table 1. K-X-ray fluorescence research: risk factors for elevated bone lead levels in studies of environmentally exposed populations.

| Study population | Risk factors identified for higher bone lead | Reference |
|------------------|--------------------------------------------|-----------|
| Queensland adults | Childhood residence in a painted wooden house | Price et al. (36) |
|                  | (lead paint), occupational exposures         |           |
| Swansee adults   | Age                                        | Morgan et al. (45) |
| Boston-area adults | Age, childhood residence in a house built prior to 1955 (lead paint) | Hu et al. (29) |
| Pennsylvania adults | Age, cumulative smoking, no breast-feeding | Kosnett et al. (37) |
| Construction workers | Age, welding/brazing, carpet laying, paint stripping, lack of exercise | Watanabe et al. (38) |
| Boston-area adolescents | Age                                      | Hoppin et al. (43) |
| Boston-area elderly men | Age, cumulative smoking, lower education | Hu et al. (39) |
| Boston-area young women | Age                                       | Hu et al. (44) |
| Mexico City women | Years living in Mexico City, lower dietary calcium | Hernandez-Avila et al. (49) |
| Boston-area elderly men | Age, cumulative smoking, lower education, lower dietary Vitamin D, lower dietary iron | Cheng et al. (51) |
| Mexico City adolescents | Higher traffic density near home, smoking by subject's mother, time spent outdoors | Farias et al. (50) |
Canada (46), parallels the age-associated increases in chemically measured bone lead levels found in autopsy studies (32,47), suggesting that bone lead rises inexorably with aging. However, because these trends were found in cross-sectional epidemiologic studies, an alternative explanation is that this represents a cohort effect, i.e., older individuals were exposed to more lead when they were as young as the younger individuals in this study. Indeed, in a 3-year follow-up study of bone lead levels in the Boston-area middle-aged and elderly men, bone lead (particularly in the patella, a trabecular bone) was uniformly declining over time (35), probably reflecting the gradual replacement of bone rich in lead (from higher earlier exposures) with bone relatively low in lead content (48). In cross-sectional studies of Mexican women (49) and adolescents (50), bone lead levels were not higher in older individuals, probably reflecting a historical trend in lead exposure that is different from that of the United States.

The development of relatively reliable and accurate semiquantitative food frequency questionnaires has also allowed studies of nutritional factors that may influence lead burden. In a further study of our cohort of Boston-area middle-aged to elderly men, we found that higher bone (but not blood) lead levels were predicted by low dietary levels of vitamin D even after adjusting for age, education, smoking, and alcohol consumption (51). This effect appeared to have a threshold around the lowest quintile of vitamin D consumption, above which bone lead levels did not vary greatly. Low dietary calcium was also predictive of higher bone lead, but the effect was not as strong as that of vitamin D. In a study of peripartum women living in Mexico City, we found that predictors of higher bone lead included time spent living in Mexico City (as opposed to rural Mexico, probably reflecting exposure to air pollution in Mexico City), and lower dietary intake levels of calcium supplements, milk, and cheese (49). These effects may reflect the impact of diet on lead absorption as well as lead kinetics.

Studies Using KXRF: Dose–Disease Relationships

Of most interest to epidemiologists interested in risks associated with disease is bone lead’s ability to serve as a biologic marker of dose and the additional information it provides, if any, beyond that provided by blood lead levels. A summary of relevant studies is provided in Table 2. Published occupational studies using KXRF have tended to focus on levels of bone and blood lead as predictors of kidney disease and urinary biomarkers of risk of kidney dysfunction. Of these, no consistent relationships have been found so far (52,53). On the other hand, several significant bone lead–disease relationships have been found in cross-sectional studies that focused on other health outcomes and used larger sample sizes and more moderately exposed subjects. Among adolescents who participated in a long-running cohort study, higher bone lead level correlated with some measures of worse performance on a neuropsychologic test battery, but its influence was not as great as that of the lead levels in deciduous teeth they had shed when young (54). Among 12-year-old boys in public school, Needleman et al. (55) found that rising tibia bone lead levels were associated with increased parental and teacher reports of delinquent, aggressive, internalizing, and externalizing behavior. In a study of moderately lead-exposed construction workers, we found that the patella (trabecular bone) is associated with significantly lower hematocrit and hemoglobin values, even after adjustment for age, smoking, and alcohol ingestion (56).

In our Superfund-supported study of middle-aged to elderly men with community exposures to lead, bone lead (but not blood lead) was significantly related to increased odds of clinically relevant hypertension, even after adjustment for age, smoking, alcohol ingestion, family history of hypertension, body mass index, dietary calcium, and dietary sodium (57). Age was associated with significantly higher odds of the occurrence of hypertension in analyses excluding bone lead; however, the effect of age decreased markedly and was not statistically significant in models that included bone lead. Our finding raises the issue of whether lack of environmental lead exposure is at least partly responsible for the lack of an age-associated increase in blood pressure and hypertension among nonindustrialized societies (58).

Subsequently, in a case–control study among Boston-area nurses, we found that bone lead, but not blood lead, was significantly related to increased odds of hypertension, even after adjustment for age, intake of dietary calcium, sodium, and alcohol, smoking, body mass index, and family history of hypertension (59). The findings of these two studies on bone lead and hypertension may explain why many of the previous studies of blood (not bone) lead and blood pressure have been negative or equivocal (60).

Among middle-aged to elderly men, higher bone lead also correlated with worse performance on specific cognitive tests (61). In this study, higher blood lead levels correlated better than bone lead levels for some outcomes, whereas higher bone lead levels correlated better than blood lead levels with other outcomes (e.g., spatial copying and pattern memory). Similar patterns were found in a recent investigation by Bleecker et al. (62) utilizing blood and bone lead levels.

In our Superfund study of lead and reproduction among women giving birth in Mexico City, we found that bone lead, but not blood lead, was significantly related to decreased birth weight, even after adjustment for maternal age, maternal arm circumference and height, smoking, parity, history of adverse reproductive outcomes, education, infant gender, and gestational.

| Table 2. K X-ray fluorescence research: bone lead as a risk factor for adverse health outcomes. |
| Study population | Outcome studied | Findings | Reference |
| Lead smelters Adolescents | Kidney dysfunction | No relationship | Gerhardsson et al. (52) |
| Construction workers | Hemoglobin, serum creatinine, blood pressure | Significant decline in hemoglobin with higher bone lead | Hu et al. (56) |
| Lead smelter workers Adolescents | Kidney dysfunction | Hyperfiltration | Roels et al. (53) |
| Elderly men | Hypertension | Increased delinquent, aggressive, internalizing, and externalizing behavior with higher bone lead | Needleman et al. (55) |
| Elderly men | Cognitive tests | Poorer performance with higher bone lead | Hu et al. (57) |
| Elderly men | Cognitive tests | Poorer performance with higher bone lead | Payton et al. (61) |
| Nurses | Hypertension | Increased with higher bone lead | Korrick et al. (59) |
| Postpartum women | Infant birthweight | Significant decline with higher bone lead | Gonzalez-Cossio et al. (63) |
Bone lead can also be compared with environmental determinants as influences on blood lead levels. In this regard, we found that bone lead retained a major influence on blood lead levels among peri-partum mothers in Mexico City, even after adjusting for current use of lead-glazed ceramics, smoking, age, occupation, years of education, parity, and years of living in Mexico City (49). Bone lead was also a significant influence on blood lead among Mexico City adolescents (50). Among middle-aged to elderly men, most of whom were retired, bone lead was the overwhelmingly predominant determinant of blood lead variance (39).

These types of studies support bone lead as a major internal source of circulating lead levels, particularly among individuals whose current environmental exposures have declined. They are complemented by KXRF studies of occupationally exposed workers. Gerhardsson et al. (64), for example, demonstrated a higher correlation between bone lead and blood lead among retired, as opposed to active, lead workers (64). Nilsson et al. (8) reported longitudinal data demonstrating a triexponential decay curve in blood lead decline following cessation of lead exposure, the slow phase of which clearly parallels the slow decline of lead in bone. Fleming et al. (65) found similar decay patterns in a KXRF investigation of lead smelter employees.

Conclusions

Although lead has been arguably the most studied toxin in environmental health, many unknowns still exist, particularly with regard to its potential to cause long-term or delayed toxicity. The development of KXRF methods for the in vivo measurement of bone lead levels has begun to enhance our ability to study this issue and the related issue as to whether mobilization of lead stored in bone may pose a significant delayed threat. Should bone lead mobilization be identified as an important risk, identifying factors that influence bone turnover, and therefore release of lead from bone, may be important in identifying strategies for mitigating the toxic effects of lead accumulated from historical exposures.

Through its ability to serve as a cumulative dosimeter, bone lead levels may also be useful in dose reconstruction studies, particularly in populations in which historical environmental or blood lead data are lacking. Initial studies on exposure–dose relationships have already demonstrated the utility of measuring bone lead as a means of identifying demographic and lifestyle factors that influence lead accumulation.

At some point in the future, if KXRF-measured bone lead is confirmed as a predictor of disease, intervention studies might be considered. It is possible, for example, that new chelating agents or strategies for inhibiting bone lead mobilization or lead–enzyme interactions may delay or reverse the progression of bone lead-associated disease. Successful interventions would warrant consideration of using KXRF, at some point, as a screening tool for certain groups of individuals at high risk.

However, large-scale screening, as is currently undertaken for potentially lead-exposed workers using blood lead levels, would be unlikely given the need for each test subject to visit a KXRF laboratory for 30 to 60 min of measurements conducted by a trained technician. In addition, although semiautomated instruments can be purchased, existing KXRF laboratories currently number fewer than 10 worldwide, are mostly oriented toward research, and require a trained physicist for set-up, calibration, and quality control in each laboratory. Finally, as noted previously, KXRF measurements in children, as compared to adults, have poor precision. Data on accumulation of lead in the bones of children are greatly needed, however, posing a challenge to researchers in this area to further improve the technical capabilities of KXRF instrumentation.

Much additional research needs to be done, and investigators in this area are grateful for the support being given for these efforts by the National Institute of Environmental Health Sciences Superfund Basic Research Program.

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