

Association of tibia lead and blood lead with end-stage renal disease: A pilot study of African–Americans

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Abstract

The association between body lead burden and kidney disease remains controversial. Fifty-five African–American end-stage renal disease (ESRD) cases and 53 age- and sex-matched African–American controls without known renal disease were recruited from Tulane University-affiliated dialysis clinics and out-patient clinics, respectively. Blood lead was measured via atomic absorption spectrophotometry and tibia lead (a measure of body lead) was measured via ¹⁰⁹Cd-based K shell X-ray fluorescence. Median blood lead levels were significantly higher among ESRD cases (6 µg/dL) compared to their control counterparts (3 µg/dL; $P < 0.001$). Although no participants had overt lead poisoning (blood lead ≥ 25 µg/dL), seven cases but no controls had blood lead levels above 10 µg/dL ($P = 0.006$). The median tibia lead level was 17 micrograms of lead per gram of bone mineral (µg/g) and 13 µg/g among ESRD cases and their control counterparts, respectively ($P = 0.134$). Four ESRD cases (7%), but no controls, had a tibia lead level above 40 µg/g ($P = 0.115$) while a similar proportion of cases and controls had tibia lead between 20 and 39 µg/g (33% and 32%, respectively; $P = 0.726$). After adjustment for potential confounders, the odds ratios of ESRD associated with a tibia lead ≥ 20 µg/g and each four-fold higher tibia lead (e.g., 5–20 µg/g) were 1.55 (95% CI: 0.55, 4.41) and 1.88 (95% CI: 0.53, 6.68), respectively. These findings support the need for prospective cohort studies of body lead burden and renal disease progression.

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1. Introduction

Occupational lead exposure at high levels is documented to induce nephropathy (Batuman, 1993; Loghman-Adham, 1997). Additionally, several community-based and clinical studies have found an association between higher blood lead levels and lower renal function (Muntner et al., 2005; Payton et al., 1994; Staessen et al., 1992; Brewster and Perazella, 2004). The nephrotoxic effects of lead may occur at very low levels. In fact, one recent study found a higher

prevalence of chronic kidney disease at blood lead levels > 2.5 µg/dL (Muntner et al., 2003).

Most epidemiologic studies investigating the nephrotoxic effects of lead in non-occupationally exposed population samples have relied on blood lead as a marker of exposure. However, with a mean biological half-life of approximately 30 days, blood lead is considered a measure of short-term lead exposure (Barry, 1975). Conversely, data indicate that bone lead is the most reliable measure of total body lead burden as it represents cumulative exposure (Rabinowitz, 1991; Hu et al., 1995). As such, bone lead can be utilized to identify persons who have been exposed to chronic low-level environmental lead over a long period of time. Hu et al. (1990) and, more recently, Weaver et al. (2005) have demonstrated the feasibility of measuring bone lead in epidemiological studies.

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Although data suggest a relationship between environmental lead exposure and the progression of renal disease, studies of body lead burden, utilizing tibia lead, and renal disease are limited. The goal of the current study was to determine the impact of long-term environmental lead exposure on the development of end-stage renal disease (ESRD). For this purpose, we conducted a case–control study including cases of ESRD, age- and sex-matched controls, and the measurement of tibia lead and blood lead concentrations.

2. Methods

2.1. Study population

Cases of ESRD were recruited from three Tulane University-affiliated dialysis clinics and controls from Tulane University-affiliated internal medicine and family medicine clinics. Cases were defined as patients receiving chronic hemodialysis treatment. A trained research assistant went to the dialysis units and provided patients an overview of the study and asked them if they were willing to participate. Those who were willing to undergo the study examination were asked questions to assess eligibility. The hemodialysis patient population at Tulane-affiliated dialysis clinics is overwhelmingly African–American. Therefore, the current study was limited to African–Americans. Overall, 36% of cases had an assigned ESRD cause of diabetes, 40% of hypertension, 6% of glomerulosclerosis, and 18% unknown. Control patients were recruited from out-patient clinics and were frequency matched on sex and 10-year age grouping (i.e., <40, 40–49, 50–59 years, etc.).

During the recruitment process, potential participants were asked if they had ever been told by a physician or other healthcare provider that they had lead poisoning. Those reporting a previous history were excluded from the current study. All women who were pre-menopausal (i.e., those reporting a menstrual cycle within the previous 12 months) received a pregnancy test due to the use of radiation in measuring tibia lead. No women were pregnant. Additionally, persons were deemed ineligible to serve as controls if they reported having received dialysis for more than 1 month during any period of their lifetime or reported having been previously diagnosed with chronic kidney disease.

2.2. Data collection

Data collection occurred during a single clinic visit to the Tulane University Office of Health Research. This clinic is dedicated to research studies, is staffed by trained and certified technicians, and follows strict quality control procedures including the routine calibration of equipment. Procedures performed during the clinic visit included participant interviews, assessment of height and weight, a blood specimen collection, and tibia lead measurement. Questionnaires were interviewer-administered and used to ascertain demographics, education, cigarette smoking, and alcohol consumption. Height was measured with a stadiometer while participants stood erect and weight was measured with an electronic digital scale while the participant was wearing light clothes. Body mass index was calculated as weight in kilograms divided by height in meters squared.

2.3. Measurement of tibia lead

Tibia lead was assessed via a 30 min measurement of the left mid-tibia diaphysis. The system employed used ^{109}Cd as the fluorescing source in a back-scatter geometry, configured with the sample, to fluoresce the K shell X-rays of lead. The lead X-rays were recorded with an intrinsic germanium detector (Canberra GL2020R, Meriden CT), quantified, and compared with calibration data to estimate the concentration of bone lead present (Todd, 2000a–d; Todd and McNeill, 1993; Todd et al., 2000,

2002). Because emitted K shell X-rays are attenuated as they pass through bone and overlying tissues, the recorded lead X-rays are normalized to the amount of elastic scattering from the bone itself resulting in a bone lead content measurement that has units of microgram (μg) of lead per gram (g) of bone mineral. This provides a measurement accuracy that is independent of several important factors such as the distance between the ^{109}Cd source and the participant, participant positioning, small movements, overlying tissue thickness, and bone size, shape, geometry, and mineral density. The method used has been described in full detail elsewhere and validated against chemical measures of lead in bone (Todd et al., 2002). All point estimates, including one negative value, were retained in the statistical analyses.

2.4. Measurement of blood lead

During the study visit, each participant provided a 14 mL blood specimen. The first 3 mL of blood was collected directly into a certified lead free Na₂ EDTA royal blue top vacutainer. This tube was kept refrigerated and shipped on the same day to Quest Diagnostics in Metairie, LA, for blood lead measurement. Blood lead levels were determined using graphite furnace atomic absorption spectrophotometry with a detection limit of 3 $\mu\text{g}/\text{dL}$.

2.5. Assessment of reliability

A 25% random sample ($n = 27$) of participants were asked to return for a second clinic visit at which time their blood lead and tibia lead were re-measured following the same protocol used for the initial study visit. The second visit took place a median of 12 days (range 1–21 days) subsequent to the first study visit.

The study protocol was approved by the Tulane University Health Sciences Center Institutional Review Board. Written informed consent was obtained from all participants prior to enrollment in the current study.

2.6. Statistical analysis

For the random sample of participants selected to have two study visits, tibia and blood lead measurements, separately, from the first visit were plotted against the second visit and Spearman's correlation coefficients were calculated. In addition, Spearman's correlation coefficient between tibia and blood lead was calculated, for all participants, and for cases and controls, separately.

The distribution of covariates were calculated for cases and controls, separately, with differences compared using *t*-tests and cross-tabulations for continuous and dichotomous variables, respectively. Due to the skewed distribution, the median and inter-quartile blood and tibia lead levels were calculated with distribution differences between cases and controls compared using the rank sum test. The blood lead and tibia lead distributions were categorized using pre-defined groupings (<5, 5–9, and ≥ 10 $\mu\text{g}/\text{dL}$ for blood lead and <20, 20–39, and ≥ 40 $\mu\text{g}/\text{g}$ for tibia lead) and compared between cases and controls by cross-tabulation. The distribution between cases and controls for blood lead overlapped only marginally, preventing further investigation. The odds ratio of ESRD by level of tibia lead was determined using logistic regression models. Initially, the age–sex adjusted odds ratio of ESRD was calculated. Subsequently, the odds ratio was calculated after additional adjustment for the potentially confounding effects of education, current and former smoking, alcohol consumption, and body mass index. To garner greater statistical power, tibia lead was analyzed as a continuous variable. For these analyses, tibia lead was natural log transformed due to its skewness and tibia lead levels less than or equal to zero ($n = 3$) were assigned a value of one, permitting log transformation. For the analysis of tibia lead as a continuous variable, the odds ratio of ESRD is presented for a four-fold increase in tibia lead (e.g., 5–20 $\mu\text{g}/\text{g}$) after calibrating the regression coefficients to account for measurement error (Rosner et al., 1989). All

data management and analysis were conducted using SAS (version 9.1; SAS Institute, Cary, NC).

3. Results

On average, ESRD cases and their control counterparts were 49.3 and 48.9 years of age, respectively, and 50.9% and 49.1%, respectively, were female indicating successful matching (Table 1). Cases were less likely than their age- and sex-matched controls to have completed high school and smoke cigarettes, although these differences were not statistically significant. In contrast, cases were non-significantly more likely to consume alcohol. Body mass index was significantly higher among controls ($P < 0.001$). The median blood lead level was significantly higher among ESRD cases compared to their control counterparts (6 $\mu\text{g}/\text{dL}$ versus 3 $\mu\text{g}/\text{dL}$; $P < 0.001$). The median tibia lead level was 17 $\mu\text{g}/\text{g}$ in ESRD cases and 13 $\mu\text{g}/\text{g}$ in their age- and sex-matched control counterparts ($P = 0.134$). Overall, the range of blood lead was 3 $\mu\text{g}/\text{dL}$ (i.e., the lower limit of detection for the assay employed) to 21 $\mu\text{g}/\text{dL}$ and the tibia lead range was 14 to 79 $\mu\text{g}/\text{g}$.

A high correlation was present between the first and second blood lead measurement ($\rho = 0.95$; $P < 0.001$) and tibia lead measurement ($\rho = 0.65$; $P < 0.001$) for the participants randomly selected to participate in a second clinic visit (Fig. 1). Additionally, the correlation between tibia lead and blood lead for the full study population was 0.48 ($P < 0.001$; data not shown) and was higher among case participants ($\rho = 0.55$) compared to control participants ($\rho = 0.17$; $P = 0.023$).

Fig. 2 shows the distribution of blood lead (left panel) and tibia lead (right panel) into pre-defined levels. Only 5.8% of controls had a blood lead between 5 and 9.9 $\mu\text{g}/\text{dL}$ and none had a blood lead equal to or greater than 10 $\mu\text{g}/\text{dL}$. In contrast, 66.7% and 14.8% of ESRD cases had blood lead levels between 5 and 9.9 $\mu\text{g}/\text{dL}$ and equal to or greater than 10 $\mu\text{g}/\text{dL}$, respectively. Also, 32.1% of controls and 32.7% of cases had tibia lead between 20

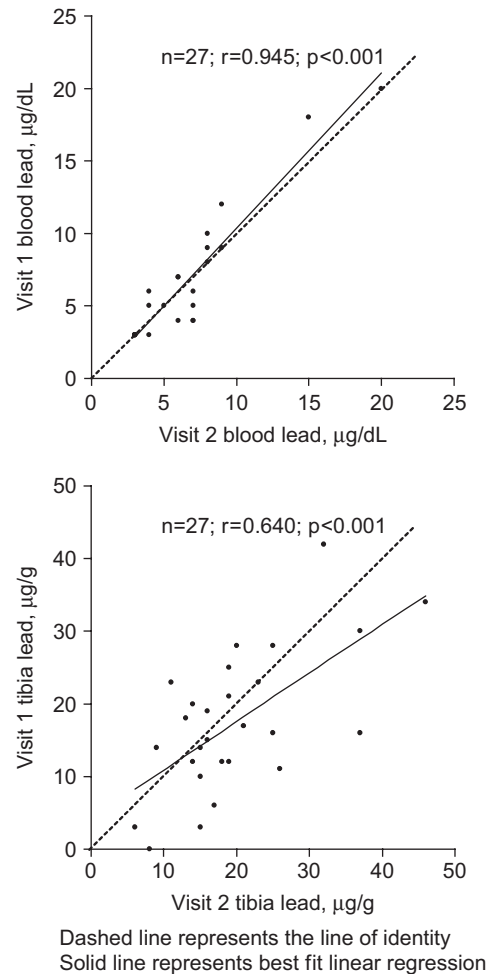


Fig. 1. Correlation between repeated blood and tibia lead measurements.

and 39.9 $\mu\text{g}/\text{g}$; no controls and 7.3% of cases ($n = 4$) had tibia lead levels ≥ 40 $\mu\text{g}/\text{g}$ ($P = 0.115$).

The odds ratios of ESRD associated with tibia lead are shown in Table 2. After adjustment for age and sex, the odds ratio of ESRD associated with a tibia lead ≥ 20 $\mu\text{g}/\text{g}$ was 1.49 (95% CI: 0.61, 3.65). Also, each four-fold higher tibia lead (e.g., 5–20 $\mu\text{g}/\text{g}$) was associated with a 2.19 (95% CI: 0.69, 6.91) times higher risk of ESRD. After additional adjustment for a high-school education, current and former smoking, alcohol consumption, and body mass index, the odds ratio of ESRD was 1.55 (0.55, 4.41) for persons with tibia lead ≥ 20 $\mu\text{g}/\text{g}$ and 1.88 (0.53, 6.68) for each four-fold higher tibia lead.

4. Discussion

The current study was designed to evaluate the relationship of tibia lead and blood lead with ESRD. A very striking relationship was present for blood lead; the entire blood lead distribution was shifted upward among ESRD cases compared to their age- and sex-matched controls. In addition, after multivariate adjustment, ESRD cases were 1.55 times more likely to have tibia lead levels

Table 1
Participant characteristics by end-stage renal disease status

	ESRD cases ($n = 55$) Mean (SD) or %	Controls ($n = 53$) Mean (SD) or %	P -value
Age, years	49.3 (1.8)	48.9 (1.7)	0.869
Female (%)	50.9	49.1	0.847
Completed high school (%)	29.1	35.9	0.453
Current smoking (%)	18.2	24.5	0.421
Consume alcohol (%)	32.7	24.5	0.346
Body mass index (kg/m^2)	27.6 (0.8)	32.6 (1.1)	<0.001
Blood lead ($\mu\text{g}/\text{dL}$) ^a	6 (5–8)	3 (3–3)	<0.001
Tibia lead ($\mu\text{g}/\text{g}$) ^a	17 (11–24)	13 (10–20)	0.134

Abbreviation: ESRD: end-stage renal disease, SD: standard deviation.

^aMedian (inter-quartile range).

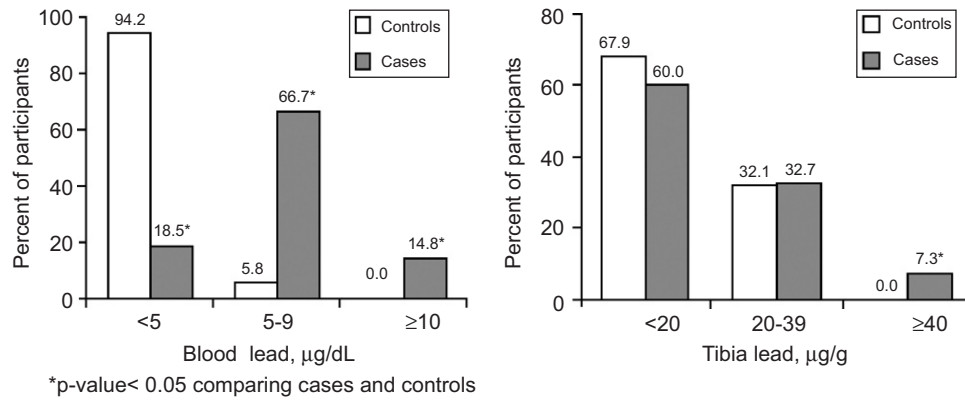


Fig. 2. Distribution of blood lead (left panel) and tibia lead (right panel) into a priori defined groupings for end-stage renal disease cases and age- and sex-matched controls.

Table 2
Odds ratios and 95% confidence intervals of end-stage renal disease associated with tibia lead ≥ 20 µg/g and a four-fold higher tibia lead level

Outcome	Tibia lead ≥ 20 µg/g	Four-fold increase in tibia lead
Adjusted for Age and sex	1.49 (0.61, 3.65)	2.19 (0.69, 6.91)
Multivariate ^a	1.55 (0.55, 4.41)	1.88 (0.53, 6.68)

^aMultivariate models are adjusted for age, sex, high-school education, current and former smoking, alcohol consumption, and body mass index.

≥ 20 µg/g compared to their age- and sex-matched control counterparts. However, it must be noted that the association of tibia lead with ESRD was not statistically significant.

The association between lead and renal disease is biologically plausible. A causal association between overt lead poisoning and the development of kidney disease has long been recognized (Brewster and Perazella, 2004). A key clinical presentation in acute lead poisoning is the presence of aminoaciduria, glycosuria, phosphaturia, and increased urinary excretion of D-ALA. In conjunction with these observations, histological changes in the setting of acute lead poisoning are noticed in the proximal convoluted tubules. Several different pathological changes occur in chronic lead nephropathy (Bernard and Becker, 1988). In some patients, the presentation of chronic lead exposure includes shrunken kidney mass, renal tubular defects, and arteriolar sclerosis. Additionally, renal cortices are atrophied with loss of glomeruli and interstitial fibrosis. Several small studies from Taiwan suggest that the nephrotoxic effects of chronic lead exposure are reversible (Lin et al., 2003, 2006a, b). Additional studies on the reno-protective benefits of EDTA therapy are warranted.

Several previous studies have investigated the association of blood lead with renal function. For example, in the population-based Cadmibel study, Staessen et al. (1992) showed that each 10-fold increase in blood lead level was associated with a 13 mL/min and 30 mL/min lower estimated creatinine clearance rate among men and women,

respectively. Also, the association of blood lead and renal function was examined in a nationally representative sample of the United States population who participated in NHANES III. After multivariate adjustment, compared to their counterparts with blood lead less than 2.5 µg/dL, the odds ratios (95% confidence interval) of chronic kidney disease for persons with a blood level between 2.5 and 3.8, 3.9 and 5.9, and ≥ 6.0 µg/dL were 1.44 (1.00, 2.09), 1.85 (1.32, 2.59), and 2.60 (1.52, 4.45), respectively (Muntner et al., 2003).

Two studies of the nephrotoxic effects of body lead burden assessed using X-ray fluorescence or EDTA lead mobilization have been published recently (Lin et al., 2003; Tsaih et al., 2004). Lin et al. (2003) followed 121 Taiwanese patients with a serum creatinine between 1.5 and 3.9 mg/dL without a potentially reversible cause (e.g., drug-induced nephrotoxic effects), no known history of lead or heavy metal exposure, for 48 months. Seventeen patients reached the primary outcome (doubling of serum creatinine or initiation of hemodialysis); 15 of them had a “high-normal” body lead burden (i.e., between 80 and 600 µg of lead based on the EDTA mobilization test), while two had a “normal” body lead burden (i.e., <80 µg of lead; $P < 0.001$). In this study, after multivariate adjustment, each 10 µg higher body lead burden was associated with a subsequent decline in GFR of 1.3 mL/min/1.73 m² ($P = 0.002$). In a study by Tsaih et al. (2004), blood lead was measured and, using X-ray fluorescence, tibia and patella lead were measured between 1991 and 1995 among 707 participants in the normative aging study of whom 448 had a serum creatinine measured 4–8 years later. In this study, higher levels of blood lead, tibia lead, and patella lead at baseline were associated with non-significantly greater increases in serum creatinine during follow-up.

It has been well established that skeleton contains approximately 95% of the body’s lead burden (Barry and Mossman, 1970). Lead in bone is primarily contained within long-lived compartments of cortical and trabecular bone with only small amounts in tissue compartments that rapidly exchange with extracellular fluid and plasma (Todd

and Chettle, 1994; Todd, 2002). Lead in bone has a half-life of several decades and, therefore, X-ray fluorescence of the (cortical) tibia is considered an excellent method for measuring lifetime lead exposure. In the current study, we used a particular X-ray fluorescence method that has been directly validated via human cadaver legs. We also conducted repeat tibia lead measurements and ran daily calibration (Todd et al., 2002) measurements using lead-doped plaster of paris phantoms. Also, the reliability of the tibia lead measurement technique is excellent. In the current study, Spearman's correlation coefficient for the two tibia lead measurements was 0.65. While this correlation is much lower than that reported previously, it is impressive given the relatively narrow range of tibia lead in the current study Todd et al. (2000). Additionally, the mean difference between the two measurements was 1.5 $\mu\text{g/g}$ ($\text{SD} = 9.5$) indicating no bias beyond that expected to be observed by chance.

The observation of significantly higher blood lead but only marginally higher tibia lead among ESRD cases compared to their control counterparts in the current study warrants particular attention. This finding raises the possibility that high bone turnover in the context of renal disease results in substantial increases in blood lead levels. Supporting this finding is the higher correlation present between tibia lead and blood lead levels among case participants compared to control participants. One previous study found a significant correlation ($\rho = 0.22$; $P = 0.01$) between parathyroid hormone and blood lead in hemodialysis patients (Colleoni et al., 1993). Future studies of tibia lead among patients with renal disease should endeavor to capture measures of bone turnover including bone density via dual energy X-ray absorptiometry, parathyroid hormone, serum calcium, and serum phosphate.

Previous studies have documented a positive public health impact from the removal of lead in gasoline and paint and the banning of lead soldered cans in the United States (Pirkle et al., 1994). However, lead exposure remains an environmental health problem among the general population in the United States. A continued diligent effort to eliminate lead pollution in the United States, especially targeting vulnerable communities, may provide additional public health benefits. Available strategies for the reduction of lead exposure include the use of safe lead paint removal practices, and clean-up of lead contaminated dust and soil.

Given the lack of prospective follow-up, caution should be taken when making causal inferences based on these study results. However, the tibia lead measurement captures lifetime cumulative lead exposure, providing confidence that at least some of the lead exposure occurred prior to the development of ESRD. Another limitation is the use of prevalent ESRD cases. Given the high rate of mortality associated with ESRD and an increased mortality at elevated blood lead levels, the association of elevated lead levels with ESRD incidence may be stronger than we

report (Foley et al., 1998; Sarnak et al., 2003; Lustberg and Silbergeld, 2002). An additional limitation is that the sample size may have been too small to detect statistically significant differences in tibia lead levels between the cases and controls. In designing the study, a goal was set to detect a 6.7 $\mu\text{g/g}$ difference in tibia lead between ESRD cases and controls. With the anticipated standard deviation of tibia lead measurement of 12 $\mu\text{g/g}$, 80% statistical power was available to detect this difference. Given the observed tibia lead difference between ESRD cases and controls of 4.0 $\mu\text{g/g}$ and the observed tibia lead standard deviation of 12.8 $\mu\text{g/g}$, a sample size of 162 ESRD cases and 162 controls would have been needed to achieve 80% statistical power. The limited sample size also prevented further investigations of the tibia lead–ESRD association across sub-groups. Finally, stored serum that was intended for creatinine measurement in control participants thawed and was ruined in the aftermath of hurricane Katrina. While no controls were on dialysis, we cannot be entirely certain that the control patients did not have sub-clinical kidney disease. However, if some controls had sub-clinical kidney disease, the true association between lead and kidney disease is stronger (i.e., the odds ratio is larger in magnitude) than we report.

The current study adds important new data on the nephrotoxic effects of environmental lead exposure. Specifically, blood lead levels were strikingly higher among ESRD cases compared to their age- and sex-matched control counterparts. Additionally, tibia lead levels, a marker of low-level chronic lead exposure, were non-significantly higher among ESRD cases compared to controls. Prospective studies of patients with chronic kidney disease that include the measurement of tibia lead are needed to better characterize the nephrotoxic effects of lead exposure. Given the potential availability of therapeutic interventions, understanding the causal impact of lead exposure on renal disease has important public health relevance.

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