Comparison of Patella Lead With Blood Lead and Tibia Lead and Their Associations With Neurobehavioral Test Scores

Carrie D. Dorsey, MD, MPH
Byung-Kook Lee, MD
Karen I. Bolla, PhD
Virginia M. Weaver, MD, MPH
Sung-Soo Lee, MD
Gap-Soo Lee, MD
Andrew C. Todd, PhD
Weiping Shi, MS
Brian S. Schwartz, MD, MS

Objective: *Lead exposure in adults is associated with worse cognitive function in cross-sectional and longitudinal studies. Previous studies have mainly examined relations with blood lead or cortical bone lead; few have examined trabecular bone lead.* ***Methods:*** *We performed a cross-sectional analysis of the relations of patella lead and other lead biomarkers with measures of neurobehavioral and peripheral nervous system function in 652 lead workers.* ***Results:*** *Patella lead was found to be associated with worse performance on seven of 19 tests of manual dexterity, sensory vibration threshold, and depressive symptoms. The associations of patella lead with cognitive function were essentially similar to those with blood lead or tibia lead but of somewhat lower magnitude.* ***Conclusions:*** *In this study, measurement of patella lead did not aid causal inference regarding cognitive effects when compared with blood lead and tibia lead.* (J Occup Environ Med. *2006;48: 489–496*)

From the Division of Occupational and Environmental Health, Department of Environmental Health Sciences (Dr Dorsey, Dr Weaver, Dr Schwartz) and the Department of Epidemiology (Dr Schwartz), Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; the Departments of Medicine (Dr Dorsey, Dr Weaver, Dr Schwartz) and Neurology (Dr Bolla), Johns Hopkins School of Medicine, Baltimore, Maryland; the Institute of Industrial Medicine (Dr Lee, Dr Lee, Dr Lee), Soonchunhyang University Chonan, South Korea; and the Department of Community and Preventive Medicine (Dr Todd), Mount Sinai School of Medicine, New York, NY.

Address correspondence to: Byung-Kook Lee, MD, Soonchunhyang University, College of Medicine, 646 Eupnae-ri, Shinchang-myun, Asan-Si, Choongnam, 336-745, Korea; E-mail: bklee@sch.ac.kr.

DOI: 10.1097/01.jom.0000199678.86629.3b

Lead distributes in the body into three pools: blood, soft tissue, and bone. Because the characteristic residence time of lead in the blood is approximately 30 days, blood lead is primarily an estimate of recent dose, but is also in equilibrium with bone lead stores.[1] With the development of x-ray fluorescence (XRF) systems, lead levels in bone have been easier to obtain. Tibia lead, representative of cortical bone, has a residence time of 25 to 30 years and serves as a biomarker of cumulative dose.[2] Trabecular bone lead is measured at sites such as the patella, calcaneus, and finger. The clearance of lead from the patella is characterized by more complex kinetics; some authors have identified two or three phases of elimination with clearance half-times ranging from months to years.[3,4] Thus, lead in the patella is often considered to be a biomarker of bioavailable lifetime dose that encompasses aspects of both accumulation and short-term bioavailability.[5]

Studies that contrast associations of health effects with different lead biomarkers that estimate pools of lead with varying kinetics and bioavailability can assist with causal inference and help interpret the conflicting evidence in the published literature. For example, two recent meta-analyses have been published, which have evaluated the association of moderate blood lead levels and neurobehavioral test scores. Both analyses attempted to make inferences about the cognitive effects of lead around blood lead levels of 70 μg/dL because of proposed changes

TABLE 1
Summary of Features of Epidemiologic Studies That Have Examined Associations of Trabecular Bone Lead With Neurocognitive Function

	Sample		Population			
Study	Size	Design	Percent Male	Race/Ethnicity	Age Mean (SD)	Outcomes
Occupational inorganic lead exposure						
Österberg 1997[10]*	38	Cross-sectional	100	Swedish	Low 41 (25–61) High 42 (24–60)**	36 NBT 4 questionnaires for symptoms
Hänninen 1998[11]†	54	Cross-sectional	80	Finnish	Low 41.7 (9.7) High 46.6 (6.2)	13 NBT
Nonoccupational lead exposure^^						
Payton 1998[12]‡	141	Cross-sectional	100	94% white, 2% black, 4% missing or other§§	66.8 (6.8)	11 NBT
Rhodes 2003[15]§	526	Cross-sectional	100	94% white, 2% black, 4% missing or other§§	67.1 (7.2)	Psychiatric symptoms
Wright 2003[16]^	736	Cross-sectional	100	94% white, 2% black, 4% missing or other§§	68.2 (6.9)	MMSE
Weisskopf 2004[17]¶	466	Longitudinal	100	94% white, 2% black, 4% missing or other§§	67.4 (6.6)	MMSE two tests on average 3.5 yr apart

(*Continued*)

*In a population of lead workers from a secondary smelter, 38 men were divided into two subgroups based on their bone-lead concentration. High- and low-level individuals were matched to each other and an unexposed control on age, education, and job level. Lead exposure was assessed by bone lead measurements, current blood lead, the highest lead level ever measured in the individual, and the cumulative blood lead index (product of current blood lead level and duration of employment). Neuropsychologic testing and self-rating scales for psychiatric symptoms were performed.

†Fifty-four lead storage battery workers were divided into two subgroups based on maximum prior blood lead levels. If blood lead had not exceeded 2.4 μmol/L, the individual was placed in the low blood lead maximum group. Assessment of lead exposure based on medical surveillance data at the plant. Cumulative exposure was assessed by time-weighted average, maximum blood lead, and integration of the cumulative dose of blood lead over duration of exposure. Calcaneal and tibia lead levels were also measured. Neuropsychologic testing and mood and symptom rating were performed.

‡Men from the VA Normative Aging Study who were evaluated between April 1993 and March 1994 were eligible for the study and included if they had data available on blood lead level, bone lead measurements, and cognitive test results. Lead exposure was assessed by blood lead, tibial lead, and patella lead measurements. Neurocognitive testing was performed.

§Men from the VA Normative Aging Study who had their first bone lead visit between January 1, 1991, and December 31, 1995, were eligible for participation provided bone lead measures were obtained within 3 mo of completing the Brief Symptom Inventory (BSI). Blood, tibia, and patella lead levels are reported. The outcome of interest was psychiatric symptoms as assessed by the BSI.

^Participants in the VA Normative Aging Study who agreed to undergo cognitive testing also completed the Mini-Mental Status Examination. Those who also underwent bone lead measurement were included in the study.

¶Men from the VA Normative Aging Study who had at least two Mini-Mental Status Examinations and bone lead measurements available were included. The study was designed to investigate longitudinal decline in scores for tests completed on average 3.5 yr apart.

**Median (range).

††μmol/L.

‡‡μg Pb/g bone mineral mean (range).

§§From Hu H, Payton M, Korrick S, et al. Determinants of bone and blood lead levels among community-exposed middle-aged to elderly men. *Am J Epidemiol.* 1996;144:749–759.

^^All studies were completed using subjects from the VA Normative Aging Study.

¶¶95% confidence interval.

***Mean (interquartile range).

SD indicates standard deviation; NBT, neurobehavioral testing; OR, odds ratio; MMSE, mini-mental status examination.

TABLE 1
(*Continued*)

Lead Biomarker, Mean (SD)					
Blood (μg/dL)	Tibia (μg/g)‡‡	Patella (μg/g)‡‡	Other	Covariates	Findings
Low 1.6 (0.8–2.6) High 1.8 (0.9–2.1)††			Finger Low 16 (−7–49) High 32 (17–106)‡‡	Age, education, and job level were matched	No associations of bone lead or blood lead with NBT in the total lead-exposed group.
Low 1.4 (0.3) High 1.9 (0.4)††	Low 19.8 (13.7) High 35.3 (16.6)‡‡		Calcaneus Low 78.6 (62.4) High 100.4 (43.1)‡‡	Age, sex, education	Calcaneus lead levels were associated with symptoms ($P < 0.05$) in the low blood lead group. Decline in test scores in one of 13 tests for calcaneus and three of 13 for blood lead.
5.5 (3.5)	22.5 (12.2)	31.7 (19.2)		Age, education	Significant decline in test scores in one of 11 tests for patella, one of 11 for tibia, and five of 11 for blood lead.
6.3 (4.16)	21.9 (13.5)	32.1 (19.8)		Age, education, employment status, alcohol consumption	Patella lead was associated with increased risk of phobic anxiety and a combined outcomes measure OR 3.62 ($P < 0.05$) vs OR 2.91 for blood lead.
4.5 (2.5)	22.4 (15.3)	29.5 (21.2)		Age, education, alcohol consumption	OR 2.1 (1.1–1.4)¶¶ for MMSE <24 comparing the highest quartile of patella lead with the lowest as the reference vs 3.4 for blood lead.
5 (3, 5)***	19 (12, 26)***	23 (15, 35)***		Age, education, alcohol consumption, smoking, time between tests	A 20-μg/g increase in patella lead was associated with a −.24 (−.44–.05)¶¶ change in MMSE. The change for blood lead was −0.01

in lead regulations in Germany.[6,7] Meyer-Baron and Seeber concluded that blood lead levels of approximately 40 μg/dL were associated with deficits in neurocognitive function.[6] In contrast, Goodman et al, in an analysis supported by the German lead industry, concluded that the data available were insufficient and inconsistent to make conclusions about the neurobehavioral effects of lead at blood lead levels less than 70 μg/dL.[7] Inferences regarding cumulative dose have been addressed by Balbus-Kornfeld et al who reviewed 21 studies to determine if cumulative exposure to lead was associated with chronic neurobehavioral dysfunction and concluded that there were no studies that had adequately addressed the question.[8] Since that review, several studies have examined relations of tibia lead, a biomarker of cumulative lead dose, with neurobehavioral test scores, but conclusions have been inconsistent across studies.[9–14]

Six studies have examined associations of trabecular bone lead with neurobehavioral test scores.[10–12,15–17] Study design, study populations, neurobehavioral outcomes, and conclusions have varied across studies (Table 1). Two studies were conducted in occupationally exposed individuals; Österberg[10] measured finger bone lead in 38 Swedish workers and Hänninen[11] investigated calcaneus bone lead in 54 Finnish workers. Relations between trabecular bone lead and neurobehavioral function were not strong and were not consistent across the two studies.

In studies of the population reported here, we have reported that blood lead was a better predictor of neurobehavioral test scores at cross-section than was tibia lead.[18] In longitudinal analyses, blood lead levels were associated with baseline test scores; change in blood lead levels was associated with change in test scores, and tibia lead was associated with test score declines over time.[19] Now, we present relations of patella lead with neurobehavioral test scores and compare those relations with those obtained for blood lead and tibia lead in the 652 Korean inorganic lead workers who completed patella lead measurement. To our knowledge, this is the largest study of occupational lead exposure that has evaluated relations of different lead biomarkers with cognitive function.

Materials and Methods

Study Overview and Design

The results presented in this report are from a cross-sectional analysis of data from the third year of a 3-year longitudinal study of Korean lead

workers. The study aims, population, and design have been previously described[18–23]; in brief, 803 lead-exposed workers and 135 control subjects were enrolled between October 24, 1997, and August 19, 1999. For this report, the 652 lead-exposed workers who completed the third visit—the visit during which patella lead levels were measured—were included. The study was reviewed and approved by the Institutional Review Boards at the Johns Hopkins School of Hygiene and Public Health (Baltimore, Maryland) and the Soonchunhyang University School of Medicine (Chonan, South Korea).

Study Population

Lead-exposed workers were recruited from 26 facilities. Participation was voluntary and subjects received approximately $30 for their participation. Written informed consent was obtained from each subject. Participation was >80% in all but four of the sites. Because of plant closings during the study, 200 individuals at the third study visit were no longer working in lead-exposed jobs.

Data Collection

Detailed descriptions of the data collection procedures have been previously published.[18–23] In brief, study participants completed a standardized interview and neurobehavioral test battery; blood pressure measurements were made; venipuncture was performed; and a urine sample was obtained. Tibia lead levels were measured at visits 1 and 2, patella lead at visit 3, and blood lead levels at all three visits. The details of the neurobehavioral testing have been presented elsewhere[18,19] but, in brief, consisted of 14 neurobehavioral tests in six cognitive domains, four peripheral nervous system (PNS) measures and one measure of psychiatric symptoms. Test scores were reviewed by a neuropsychologist before modeling and scores not thought to be physiologically plausible were excluded from the analysis.[18]

Laboratory Methods

Blood lead levels were measured using a Zeeman background-corrected atomic absorption spectrophotometer (model Z-8100; Hitachi Ltd., Tokyo, Japan).[24] Tibia and patella lead were measured in micrograms of lead per gram of bone using ^{109}Cd-induced K-shell x-ray fluorescence (XRF) using previously reported methods.[18–23] Thirty-minute measurements were taken from the left midtibia shaft and the left patella.

Statistical Analysis

The primary goals of the analysis were to: 1) evaluate associations of patella lead levels with neurobehavioral test scores, measures of PNS function, and the psychiatric symptom measure; and 2) to compare patella lead with tibia lead and blood lead in their associations with test scores. Linear regression modeling was used to evaluate associations between the lead biomarkers and test performance. The outcomes were standardized so that a higher test score always indicated better performance. The 19 outcomes were modeled separately for each biomarker. Age, gender, and education were controlled for in all models. In addition, when modeling the PNS sensory outcomes, height was included in the models, and for the PNS motor outcomes, body mass index was included.[18,19] Additional covariates that were not significant predictors of test scores nor confounders of the relations between lead variables and test scores were not retained in the models. These covariates included tobacco use, alcohol consumption, former versus current lead exposure, type of lead-using facility, blood lead adjusted for hematocrit, and quadratic terms for the lead biomarkers (for assessment of nonlinear relations).

Patella, blood, and tibia lead were modeled nonparametrically (as percentiles after ranking) to account for extreme deviations from normality for the patella lead measurements and to allow for the magnitude of relations to be compared among the three biomarkers. Blood lead measurements for visit three and tibia lead measurements obtained at visit two on 574 study participants were used for the analysis. The following models were evaluated: (model 1) blood lead, tibia lead, or patella lead alone; (model 2) blood lead and tibia lead or blood lead and patella lead; (model 3) blood lead and job duration, mean tibia lead and job duration, or patella lead and job duration; and (model 4) blood lead, tibia lead, and job duration or patella lead, blood lead, and job duration. To simplify presentation of results, only those from model 3 are presented but the results of the other models are discussed. Model 3 was chosen for comparison because it includes job duration, which was previously shown to merit inclusion in the final models because it strengthened the relations with tibia lead levels, thought to be due to possible selection bias and dropout among workers with higher tibia lead levels.[18]

Preliminary analysis of the patella lead levels revealed a wide range of values and nonnormality, and inferences regarding the associations with test scores were influenced by outliers. Examination of added variable plots of the residuals of patella lead versus neurobehavioral test scores confirmed that these models did not meet the assumptions for use of linear regression modeling. After transformation, examination of models with ranked patella in added variable plots supported use of ranked patella for these models.

In addition to presenting adjusted regression lines, the lowess smoothing function was used to make estimations of the associations of lead biomarkers to neurobehavioral test scores.[25]

Results

Demographic Data and Dose Measures

For the 652 current and former lead workers, the mean (standard

TABLE 2
Characteristics and Lead Biomarker Levels in Korean Lead Workers at the Third Study Visit, 1999–2001

Characteristic	Lead-Exposed Subjects (N = 652)		
	Mean	Standard Deviation	Range
Age, yr	43.4	9.6	20–67.7
Lead work job duration, yr	10	6.5	0.1–36.3
Blood lead, μg/dL	30.9	16.7	4–89.3
Patella lead, μg Pb/g bone	75.1	101.1	−11.8–946.1
Tibia lead, μg Pb/g bone*	33.5	43.4	−17.8–334.0

*Tibia lead measured at visit two among subjects who had patella lead measured at visit 3 (N = 574).

deviation [SD]) age was 43.3 (9.6) years and mean job duration was 10.0 (6.5) years (Table 2). The mean (SD) levels for the lead biomarkers were 30.9 (16.7) μg/dL, 75.1 (101.1) μg/g, and 33.6 (43.4) for blood lead (visit 3), patella lead (visit 3), and tibia lead (visits 2), respectively. When compared with subjects who did not complete visit three, there were significant differences in age and job duration. Visit three noncompleters were younger 37.8 (11.4) years ($P < 0.01$) and had a shorter duration of employment (mean job duration of 6.6 [6.7] years) ($P < 0.01$). There were no differences in blood lead levels between completers and noncompleters ($P = 0.69$). Tibia lead was highly correlated with patella lead levels (Pearson's r = 0.89 and Spearman's r = 0.76); the correlation of patella lead and blood lead was lower (Pearson's r = 0.53 and Spearman's r = 0.66). As patella lead levels increase, the relation with blood lead levels plateaus (Fig. 1), as demonstrated by the lowess line on the plot.

Patella Lead Levels and Neurobehavioral and Peripheral Nervous System Measures

Next, the four linear regression models were evaluated with ranked patella. For "model 1," coefficients for the ranked patella term were neg-

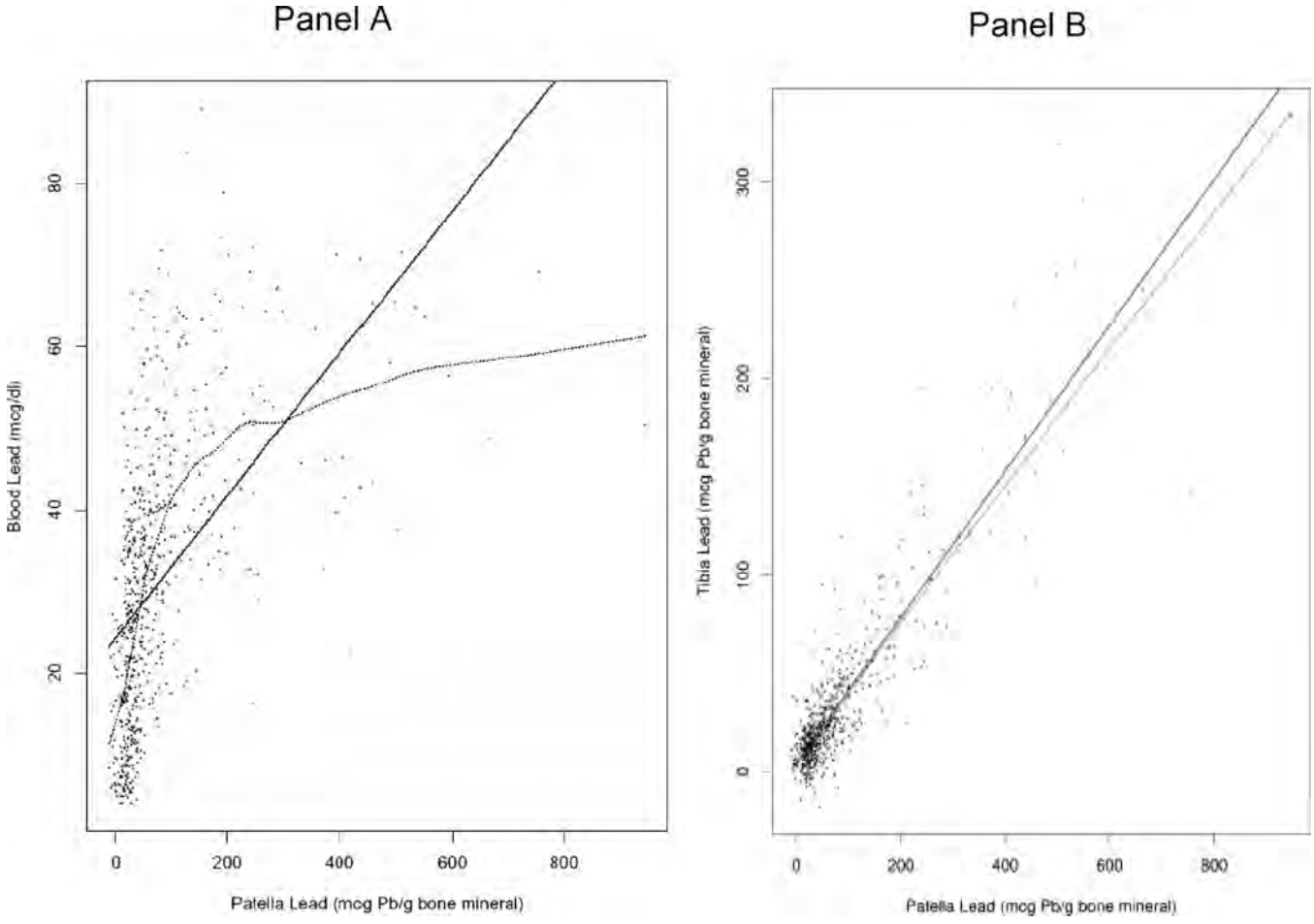

Fig. 1. Correlation of patella lead measurements to blood lead levels (**A**, N = 652) and tibia lead (**B**, N = 574) measurements in 652 Korean lead workers who completed visit three of a 3-year longitudinal study. The solid lines are from linear regression. The dotted lines represent estimations made by the lowess smoothing method.[24]

TABLE 3
Adjusted Linear Regression Modeling of Associations of Neurobehavioral and Peripheral Nervous System Measures With Lead Biomarkers, Republic of Korea, 1999–2001

Domain and Neurobehavioral Test	Ranked Patella Lead§ˆ¶ β	Ranked Patella Lead§ˆ¶ SE	Ranked Blood Lead§ˆ¶ β	Ranked Blood Lead§ˆ¶ SE	Ranked Tibia Lead§ˆ** β	Ranked Tibia Lead§ˆ** SE
Psychomotor speed						
Simple reaction time (ms)	−0.0002	0.0003	−0.0001	0.0002	−0.0007	0.00003†
Simple reaction time SD (root MSD)	0.0003	0.0008	0.0005	0.0008	0.0000	0.0008
Executive abilities						
Trail-making test A (seconds)	−0.0003	0.0006	−0.0005	0.0005	−0.0012	0.0006†
Trail-making test B (seconds)	−0.0006	0.0005	−0.0008	0.0005*	−0.0010	0.0006*
Digit symbol substitution (no. correct)	−0.0216	0.0183	−0.0275	0.0168	−0.0462	0.0185†
Purdue pegboard, assembly (no. of pieces)	−0.0225	0.0101†	−0.0239	0.0092‡	−0.0281	0.0101‡
Verbal memory and learning						
Digit span test, total (no. correct)	−0.0026	0.0058	−0.0042	0.0054	−0.0044	0.0059
Visual memory						
Benton visual retention (no. correct)	0.0015	0.0025	−0.0005	0.0023	−0.0013	0.0025
Nonverbal intelligence						
Colored progressive matrices (no. correct)	−0.0045	0.0079	−0.0111	0.0072	−0.0000	0.0080
Manual dexterity						
Pursuit aiming test (no. correct)	−0.0612	0.0346*	−0.0859	0.0316‡	−0.0824	0.0357†
Pursuit aiming test (no. incorrect)	0.0058	0.0343	−0.0123	0.0314	0.0109	0.0351
Purdue pegboard, dominant hand (no. of pieces)	−0.0055	0.0029*	−0.0073	0.0027‡	−0.0103	0.0029‡
Purdue pegboard, non dominant hand (no. of pieces)	−0.0077	0.0028‡	−0.0074	0.0026‡	−0.0082	0.0028‡
Purdue pegboard, both hands (no. of pieces)	−0.0086	0.0026‡	−0.0084	0.0024‡	−0.0101	0.0025‡
Neuropsychiatric status						
CES-D (no. of frequency-ranked symptoms)	−0.0335	0.0123‡	−0.0041	0.0113	−0.0303	0.0124†
PNS sensory–vibration threshold						
Nondominant index finger (vibration units)‡‡	−0.0001	0.0008	0.0005	0.0007	−0.0009	0.0008
Dominant great toe (vibration units)	−0.0023	0.0007‡	−0.0017	0.0006‡	−0.0019	0.0007‡
PNS motor strength						
Grip strength (kg), non dominant hand	0.0009	0.0124	0.0279††	0.0113†	−0.0071	0.0125
Pinch strength (kg), nondominant hand	−0.0026	0.0027	0.0008	0.0024	−0.0042	0.0026

*$P < 0.10$.
†$P < 0.05$.
‡$P < 0.01$.
§All models controlled for age, gender, education, and job duration. Models of the PNS sensory measures also included height; models of the PNS strength measures also included body mass index. All outcomes have been standardized, so a negative β coefficient indicates that performance was worse with increasing lead biomarker levels.
ˆRanked values obtained by percentile ranking of the lead biomarkers. β coefficients represent the change in neurobehavioral test score for a one-percentile change in the rank of the biomarker.
¶Patella lead and blood lead measured at visit three.
**Tibia lead measurements taken at visit two (only includes values for those subjects completing visit three).
††Significant predictor of better performance.
‡‡Vibration unit = 1/2 (amplitude [μ])^2.
SE indicates standard error; SD, standard deviation; MSD, mean square deviation; CES-D, Center for Epidemiologic Studies–Depression scale; PNS, peripheral nervous system.

ative and had associated *P* values ≤0.10 for two of 14 neurobehavioral measures, one PNS measure, and the symptom score (data not shown), providing only limited evidence of an association between patella lead and neurobehavioral or PNS function. Associations with patella lead were dramatically reduced after addition of blood lead to the models. There was an association with only the symptom score (model 2, data not shown). After addition of job duration and removal of blood lead (model 3, data presented in Table 3 under "ranked patella" column), there were associations (at a significance level <0.10) of patella lead with five tests in the domain of manual dexterity, the PNS sensory vibration threshold (dominant great toe), and Center for Epidemiologic Studies–Depression (CES-D). All beta coefficients were negative, indicating an adverse effect. After addition of blood lead to model three, associations with patella lead were fewer and involved only the PNS sensory function and neuropsychiatric status as measured by symptoms (data not shown); only two associations remained significant at a level of $P < 0.10$.

Comparison of Lead Biomarkers

Comparison of the associations of patella lead, tibia lead, and blood lead (modeled as ranked values) with neurobehavioral test scores were evaluated in terms of significance, magnitude, and consistency of the associations within and across domains. As seen in Table 3, tibia lead was significantly associated ($P < 0.10$) with worse performance on 11 tests. Blood lead and patella lead were both associated with worse performance on seven of the tests. When evaluating consistency within and across domains, patella lead behaved similarly to both blood lead and tibia lead in the domains of manual dexterity, executive abilities, neuropsychiatric status, and PNS sensory function. Tibia lead was more consistent in the domain of executive abilities and, unlike patella and blood lead, also was associated with poorer performance in the domain of psychomotor speed. The magnitude for a 1% change in ranked patella estimates was generally smaller than those for blood and tibia lead.

Discussion

In this study of neurobehavioral and PNS outcomes, in models controlling for job duration, we observed consistent associations with patella lead in the areas of manual dexterity, peripheral vibration threshold, and CES-D. In comparing the three lead biomarkers, we evaluated significance, magnitude, and consistency of the associations within and across domains. We concluded that inclusion of patella lead in the study, with blood lead and tibia lead, did not provide additional information useful to causal inference. The contrasting associations suggest that both recent and cumulative dose are important predictors of neurobehavioral test scores, but patella lead, which is measured with considerable additional time and cost, was of no apparent marginal benefit.

To date, six studies have examined relations of trabecular bone lead levels with cognitive function. The studies have differed widely in design, trabecular bone measurement site, study population, sample size, covariates, and neurobehavioral assessment (Table 1).[10–12,15–17] All of the studies compared trabecular bone lead measures with blood lead and all but one[10] with tibia lead. Four of the six studies were nonoccupational and all of these used data from the Veterans Administration Normative Aging Study.[12,15–17] In two of the nonoccupational studies, patella lead was found to be a better predictor of psychiatric symptoms[15] and longitudinal decline in Mini-Mental Status Examination scores.[17] Our finding that blood lead was more strongly associated with neurobehavioral test scores than patella lead, as evidenced by the magnitude of the regression coefficients (Table 3), is consistent with those of Hänninen et al,[11] an occupationally exposed cohort, and Payton et al,[12] an environmentally exposed population. Hänninen et al similarly found significant associations of trabecular bone lead with psychiatric symptoms.[11]

In conclusion, in this large cohort of current and former lead workers, we observed associations of patella lead levels with neurobehavioral test scores in the domains of manual dexterity, sensory PNS function, and psychiatric symptoms. In conjunction with our other cross-sectional and longitudinal observations in this population,[18,19] the data suggest that lead influences neurobehavioral test scores as a function of both recent and cumulative dose, but measurement of patella lead did not aid in causal inference in this study. Although we believe the three lead biomarkers are reflective of different dose periods, in vivo pools, and kinetics, our data do not suggest that patella lead behaves significantly differently than blood and tibia lead in its associations with nervous system outcomes. The generally weaker associations with patella lead may suggest that bioavailable bone lead was less important to cognitive function in these workers than was the acute effects of recent dose, as estimated by blood lead, and the chronic effects of cumulative dose, as estimated by tibia lead. It is possible that individual neurobehavioral tests may be differentially associated with the different lead biomarkers for biologic or other reasons; however, when evaluating associations with neurobehavioral testing, it is the domains that are relevant to interpretation and the associations of patella lead were consistent with the other biomarkers and did not provide additional information. It is also possible that the weaker relations with patella lead were due to the measurement error in patella lead as previously reported.[26]

Acknowledgments

This research was supported by grants ES07198 (Dr Schwartz) from the National Institute of Environmental Health Sciences and KRF-2001-00,040 (Dr Lee) from the Korea Research Foundation.

References

1. Rabinowitz MB. Toxicokinetics of bone lead. *Environ Health Perspect*. 1991;91: 33–37.
2. Rabinowitz MB, Wetherill GW, Kopple JD. Kinetic analysis of lead metabolism in healthy humans. *J Clin Invest*. 1977; 58:260–270.
3. Legget RW. An age-specific kinetic model of lead metabolism in humans. *Environ Health Perspect*. 1993;101:598–616.
4. Tsaih S-W, Korrick S, Schwartz J, et al. Influence of bone resorption on the mobilization of lead from bone among middle-aged and elderly men: the Normative Aging Study. *Environ Health Perspect*. 2001;109:995–999.
5. Hu H, Rabinowitz M, Smith D. Bone lead as a biological marker in epidemiologic studies of chronic toxicity: conceptual paradigms. *Environ Health Perspect*. 1998;106:1–8.
6. Meyer-Baron M, Seeber A. A meta-analysis for neurobehavioral results due to occupational lead exposure with blood lead concentration <70 μg/100 ml. *Arch Toxicol*. 2000;73:510–518.
7. Goodman M, LaVerda N, Clarke C, et al. Neurobehavioral testing in workers occupationally exposed to lead: systematic review and meta-analysis of publications. *Occup Environ Med*. 2002;59:217–223.
8. Balbus-Kornfeld JM, Stewart W, Bolla

K, et al. Cumulative exposure to inorganic lead and neurobehavioral test performance in adults: an epidemiological review. *Occup Environ Med*. 1995; 52:2–12.
9. Bleecker ML, Lindgren KN, Ford DP. Differential contribution of current and cumulative indices of lead dose to neuropsychological performance by age. *Neurology*. 1997;48:639–645.
10. Österberg K, Börjesson J, Gerhardsson L, Schütz A, Skerfving S. A neurobehavioral study of long-term occupational inorganic lead exposure. *Sci Total Environ*. 1997;201:39–51.
11. Hänninen H, Aitio A, Kovala T, et al. Occupational exposure to lead and neuropsychological dysfunction. *Occup Environ Med*. 1998;55:202–209.
12. Payton M, Riggs KM, Spiro A III, Weiss ST, Hu U. Relations of bone and blood lead to cognitive function: the VA Normative Aging Study. *Neurotoxicol Teratol*. 1998;20:19–27.
13. Stokes L, Letz R, Gerr F, et al. Neurotoxicity in young adults 20 years after childhood exposure to lead: the Bunker Hill experience. *Occup Environ Med*. 1998;55:507–515.
14. Stewart WF, Schwartz BS, Simon D, Bolla KI, Todd AC, Links J. Neurobehavioral function and tibial and chelatable lead levels in 543 former organolead workers. *Neurology*. 1999;52:1610–1617.
15. Rhodes D, Spiro A, Aro A, Hu H. Relationship of bone and blood lead levels to psychiatric symptoms: the VA Normative Aging Study. *J Occup Environ Med*. 2003;45:1144–1151.
16. Wright RO, Tsaih SW, Schwartz J, et al. Lead exposure biomarkers and Mini-Mental Status Exam scores in older men. *Epidemiology*. 2003;14:713–718.
17. Weisskopf MG, Wright RO, Schwartz J, et al. Cumulative lead exposure and prospective change in cognition among elderly men: the VA Normative Aging Study. *Am J Epidemiol*. 2004;160:1184–1193.
18. Schwartz BS, Lee B-K, Lee G-S, et al. Associations of blood lead, dimercaptosuccinic acid-chelatable lead, and tibia lead with neurobehavioral test scores in South Korean lead workers. *Am J Epidemiol*. 2001;153:453–464.
19. Schwartz BS, Lee B-K, Bandeen-Roche K, et al. Occupational lead exposure and longitudinal decline in neurobehavioral test scores. *Epidemiology*. 2005;16:106–113.
20. Todd AC, Lee B-K, Lee G-S, Ahn KD, Moshier EL, Schwartz BS. Predictors of DMSA chelatable lead, tibial lead, and blood lead in 802 Korean lead workers. *Occup Environ Med*. 2001;58:73–80.
21. Schwartz BS, Lee B-K, Lee G-S, et al. Associations of blood lead, dimercaptosuccinic acid-chelatable lead, and tibia lead with polymorphisms in the vitamin D receptor and δ-aminolevulinic acid dehydratase genes. *Environ Health Perspect*. 2000;108:949–954.
22. Weaver VM, Lee B-K, Ahn KD, et al. Associations of lead biomarkers with renal outcomes in Korean lead workers. *Occup Environ Med*. 2003;60:551–562.
23. Weaver VM, Lee B-K, Todd AC, et al. Associations of patella lead and other lead biomarkers with renal function in lead workers. *J Occup Environ Med*. 2005;47:235–243.
24. Fernandez FJ. Micromethod for lead determination in whole blood by atomic absorption, with use of the graphite furnace. *Clin Chem*. 1975;21:558–561.
25. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc*. 1979;74:829–836.
26. Hu H, Milder FL, Burger DE. The use of K x-ray fluorescence for measuring lead burden in epidemiological studies: high and low lead burdens and measurement uncertainty. *Environ Health Perspect*. 1991;94:107–110.