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Associations Between Bone Mineral Density, Grip Strength, and Lead Body Burden Among Older Men

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Abstract

Objectives—To study the association of blood lead concentration (BPb) to bone mineral density (BMD), physical, and cognitive function in non-institutionalized community dwelling older men.

Design—Cross sectional study.

Setting—University of Pittsburgh clinic, Pittsburgh, PA.

Participants—Non-Hispanic Caucasian men aged 65 or older (N=445) recruited as a subset of a prospective cohort Osteoporotic Fractures in Men (MrOS) study.

Measurement—BPb was measured in 2007-2008. From 2007-2009 BMD (g/cm^2) was measured using dual energy x-ray absorptiometry (DXA). At the same time physical performance was measured with five tests: grip strength, leg extension power, walking speed, narrow-walk pace, and chair stands. Cognitive performance was assessed using the Modified Mini-Mental State Examination and the Trail Making Test Part B. Participants were categorized into quartiles of BPb. Multivariate regression analysis was used to evaluate independent relationship between BPb, BMD, cognitive and physical function.

Results—Mean ±sd BPb was 2.25±1.20 μg/dL (median =2 μg/dL, range 1-10). In multivariable adjusted models, men in higher BPb quartiles had lower BMD at femoral neck, and total hip (p-trend =<0.001 for both). Men with higher BPb had lower age adjusted score for grip strength (p-trend<0.001). However, this association was not significant in multivariate adjusted models (p-trend <0.148). BPb was not associated with lumbar spine BMD, cognition, leg extension power, walking speed, narrow-walk pace, and chair stands.

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Conclusion—Environmental lead exposure may adversely affect bone health in older men. These findings support consideration of environmental exposures in age associated bone fragility.

Keywords

lead; elderly; men; bone; grip strength; cognition; physical function

INTRODUCTION

Age related osteoporosis and decline in physical function are significant public health concerns as they are associated with falls [12], fractures [32], frailty [2] and morbidity[45]. In the United States National Health and Nutrition Examination Survey (NHANES) data completed in 2005-2008 nine percent of adults over age 50 years had osteoporosis at either the femoral neck or lumbar spine and one-half had low bone mass at one of these two bone sites[6]. It is estimated that one third of all osteoporotic fractures, and 25% of osteoporosis-related costs are observed in men[6],with higher associated mortality than in women[7]. The health care burden will increase with increasing longevity in population[7]. Therefore, it is important to identify determinants of bone strength, and physical function in older men including environmental exposures such as lead.

Lead is a toxic element highly prevalent in the environment. Lead exposure has been associated with reduced bone mineral density (BMD)[8, 9], physical function[10] and fine motor skills[11] in community exposed adults and occupational cohorts[12]. However, concurrent associations between blood lead concentration (BPb), BMD, physical and cognitive function in environmentally exposed men remain relatively unexplored. The NHANES survey from 2007-2008 showed that compared to the population mean of 1.3 μg/dL, older adults had higher BPb (1.4 μg/dL); men had higher BPb than women[13].

The skeleton stores 95% of body lead, with a half life of up to 27 years [14]. During rapid bone turnover related with aging, lead can be released into the circulation where it becomes bioavailable to exert toxic effects on target organs. The current study examined the relationship between BPb, BMD, physical and cognitive performance in a cohort of older men.

METHODS

Study population

The Osteoporotic Fractures in Men Study (MrOS) is a prospective cohort study of community dwelling non-institutionalized men in the US. Between 2000 and 2002, 5994 men at least 65 years of age were enrolled from population-based listings at six clinical sites: Birmingham, AL; Minneapolis, MN; Pittsburgh, PA; Palo Alto, CA; Portland, OR; and San Diego, CA. Eligibility criteria included the ability to walk unaided and without bilateral hip replacements.

A cross sectional study was completed from 5/4/2007 to11/12/2008 involving participants recruited as a subset of MrOS study. This ancillary BPb study was conducted in 445 Non-Hispanic Caucasian participants enrolled in MrOS at the University of Pittsburgh clinic

(Monongahela Valley near Pittsburgh). Complete data on BMD and physical performance at MrOS visit three (2007-2009) were available for these participants. The study protocol was approved by the institutional review board, and written informed consent was obtained from all the participants. Details of the MrOS study design, recruitment, and baseline characteristics have been described [15].

Data Collection and Assessment Procedures

Blood lead measurements—For lead measurement a 0.5 milliliter blood sample was taken by venipuncture according to published standardized study protocols [15]. Lead level was determined using atomic absorption spectrophotometry conducted[16] by the Special Chemistry Laboratory, an affiliate of the University of Pittsburgh Medical Center. This lab is certified for the analysis of lead in blood by the College of American Pathologists, Pennsylvania Department of Health and the Centers for Disease Control and Prevention. Lead concentrations were assayed on a PerkinElmer ELAN DRCe, Inductively Coupled Plasma Mass Spectrometer (Waltham, MA, USA). The analytical limit of detection (LoD) by the laboratory was 1 μg/dL. For ten participants with BPb concentration values below LoD, a value of 0.71 ug/dL was substituted for statistical analysis following usual practice (LoD divided by the square root of 2) [17].

Measurement of BMD—BMD (g/cm^2) at the lumbar spine, total hip and its sub region femoral neck was measured using dual energy x-ray absorptiometry (DXA) with QDR-4500 W scanners (Hologic, Inc., Bedford, MA). Antero-posterior lumbar spine BMD was measured in all men, and mean BMD was computed from the first through fourth lumbar vertebrae. Hip BMD was measured on the right side. If a right hip replacement or metal objects in the right leg were reported, the left hip was measured. The quality control of DXA measurements included certification of DXA technicians, and implementation of a standardized scanning procedure. At each study visit a hip phantom was circulated and scanned at the six clinical sites. No linear differences across scanners were detected in cross-calibration studies. The inter-scanner coefficient of variation (CV) was 0.9%. For spine BMD, maximum percent difference between scanners was 1.4% [18].

Other measurements—Self-administered questionnaires were used to ascertain participants' demographic and lifestyle information. During interviews or examinations anthropometric measures and neuromuscular function were assessed by trained study staff. Information on education was obtained (years of education completed) at baseline (2000-2002) [15]. Increasing education status is associated with decreased osteoporosis risk[19]. Lifestyle factors included self-report of smoking (current, past, and never), and alcohol intake (drinks/week). Smoking and alcohol intake are known risk factors for osteoporosis in men[20].

A calibrated balance-beam scale was used to measure participants' weight in kilograms in indoor clothing and without shoes. Height was measured in meters using a Harpenden Stadiometer (Dyfed, UK). BMI was calculated as weight in kg/height in $meters^2$. Increasing body weight is protective against osteoporosis[20].

Physical performance—Physical performance was measured with five tests: grip strength, leg extension power, walking speed, narrow-walk pace, and chair stands use arms yes/no. Grip strength was measured on a JAMAR dynamometer (Sammons Preston, Bolingbrook, Illinois). The average value (kilograms) from two trials from both hands was analyzed. Leg extension power was measured with the Nottingham power rig [21]. Leg extension power measured with this device correlates well with functional measures, such as chair-rising speed, stair-climbing speed and power, and walking speed in elderly subjects [21]. Five trials for each leg were conducted and the maximum value (watts) from either leg was analyzed.

Walking speed was assessed on a standard 6-m walking course [21]. Participants were instructed to walk at their normal pace for this examination. The fastest speed (meters/second) was analyzed. The narrow walk was used as an indirect measure of dynamic balance[21]. Participants were asked to walk a 6-meter course while keeping each foot within a 20-centimeter wide lane. A trial was considered successful if the participant had no more than two deviations from the lane. Participants were asked to do two trials. If one or both trials were unsuccessful, they were asked to do a third trial. The fastest pace (meters/second) from any successfully completed trial was analyzed [21]. Ability to stand from a chair without using the arms (yes/no) was also measured [21].

Cognitive Measures—The Modified Mini-Mental State Examination (3MS) was used to assess cognition [22] with higher scores (0-100) representing better performance. It is a global measurement of cognitive function, with components for orientation, concentration, language, praxis, and immediate and delayed memory. The Trail Making Test Part B (Trails B) is a timed test that measures attention, sequencing, visual scanning, and executive function [23]. A faster time for completion (in 0-300 seconds) represents better cognitive performance.

Statistical analysis

Distribution and normality of outcome variables, covariates and BPb was ascertained. Based on skewed distribution, BPb was log transformed (mean 2.25 μg/ dL, median 2, range 1-10). To explore possible non-linear association of outcome variables and BPb, 3 knot spline analysis was carried out on log transformed BPb (knots were placed at 25 percentile=0.0, 50^{th} percentile=0.69, 75^{th} percentile=1.09). Wald test was used to assess whether all four segments simultaneously had zero slope (p-value =<.001 for all three dependent variables). BMD at total hip, femoral neck, and grip strength showed significant non-linear relationship with BPb. However, BMD at lumbar spine, cognitive function, leg extension power, walking speed, narrow-walk pace showed linear association with BPb.

Participants' characteristics were compared by categorizing them in BPb quartiles using SAS Proc GLM for continuous variables and x^2 tests for categorical variables. These BPb categories comprised of quartile 1(≤1μg/dL; n= 126), quartile 2 (>1, ≤2μg/dL; n= 175), quartile 3 (>2, ≤3μg/dL; n= 84), quartile 4(>3μg/dL; n= 60). Further age and multivariate adjusted analysis for total hip, femoral neck, and grip strength was completed using Proc GLM across BPb quartiles (untransformed BPb). As described above in spline analysis

BMD at lumbar spine, cognitive function, leg extension power, walking speed, and narrow-walk pace demonstrated linear association with BPb. Based on this linear association with BPb, these variables were analyzed in separate age and multivariate adjusted models as continuous outcomes. Association of BPb and chair stands (use of arms, yes/no) was analyzed using logistic regression; odds ratio and 95% confidence interval was reported.

For each outcome, model building began by regressing BPb on that function, sequentially adding age, and finally adding education, smoking, alcohol consumption, and BMI simultaneously. Selection of these covariates was decided a priori based on literature and our previous work [9]. Analysis was performed using SAS 9.2 (SAS Institute, Cary, NC, USA). STATA was used for spline analysis (edition 9, StataCorp, College Station, Texas, USA). Two tailed p-values were used for all tests, at 5% statistical significance

RESULTS

Characteristics of the Participants

Mean ±sd BPb was 2.25±1.20 μg/dL (median 2, range 1-10) and mean age was 79.5±5 years (Table 1). Average age was significantly higher in men with higher BPb (p-trend=.004). BMI, education, and smoking pattern did not differ across BPb quartiles. Alcohol consumption was highest in the second quartile and decreased significantly across the rest of BPb strata (p=.015). In unadjusted models presented in table 1, men with high BPb had significantly lower mean BMD compared across quartiles 2 to 4 at femoral neck (p-trend <. 001) and total hip (p-trend=.004) respectively. Although lumbar spine BMD decreased in men in BPb quartile 2 to 4, it was not statistically significant. A significant trend of lower grip strength (p-trend =.006) across BPb quartiles 2 to 4 was seen. Although decreases in all physical and cognitive functions across BPb quartiles 2 to 4 were observed they did not reach statistical significance.

Age and multivariate adjusted models

In age adjusted models men in BPb quartiles 2-4 had lower BMD at femoral neck and at total hip (p-trend<.001 for both) (Table 2). Upon further adjustment with covariates, the significant difference persisted at femoral neck (p-trend<.001) and at total hip (p<0.004). In age adjusted models grip strength decreased across BPb quartiles 2-4 (p-trend<0.001). Although in multivariate adjusted models, the pattern of decreasing grip strength existed across BPb quartiles 2-4, it was not statistically significant (Table 2).

In age and multivariate adjusted models no significant association between BPB, lumbar spine BMD, cognitive function and physical function was noted (Table 3).

DISCUSSION

The results of this study suggest that a circulating average lead concentration of 2 ug/dL is associated with lower BMD at femoral neck and total hip in older men. However, no effect was seen on grip strength, leg power, walking speed, narrow walk pace, and chair stands, cognitive function and lumbar spine BMD. The study provides further evidence that despite

a significant decline in mean BPb in US population, older adults with higher lifetime environmental lead exposure may have some risk of adverse bone changes.

To our knowledge this is the first study to report a decrease in BMD in older men even at relatively low environmental exposure to lead. Several lines of evidence suggest that BPb may have a causative role in osteoporosis [24]. Lead is contained in the mineral matrix of bone in close proximity with calcium, mimicking many physical and chemical properties. Lead competes with calcium in intestinal absorption, transport, and bone deposition [14]. Similar to calcium, lead absorption from the intestine is regulated by parathyroid hormone and Vitamin D[14].

In this study a trend in higher BPb with increase in age was noted, possibly related to age associated osteoporosis. Mean BPb in men aged 80 or older was 2.5 ug/dL, compared to 2.1 ug/dL in 70-75 year old men (p=.004, data not shown). In the current study although BMD was tested at three bone sites, significant decrease was seen only at total hip and femoral neck which is consistent with existing research[25]. There was no association of lead exposure with lumbar spine bone density in this study. It is important to note that in the MrOS cohort (n=5,995) hip BMD declined with advancing age, while spine BMD increased[26].

In this study a significant inverse correlation was noted between BMD and BPb at total hip (r=-0.14, p= .003) and femoral neck (r=-0.14, p= .004) (results not shown). Likewise, in NHANES III a significant inverse association between BPb and BMD[25] was reported; factors related to BMD were significant predictors of BPb [8].

When bone resorption increases with age, more lead is released into the circulation. An inverse association between BPb and mechanical strength has been reported. Neurological effects of lead are principally on the large myelinated fibers producing neuropathy, axonal degeneration that impairs nerve conduction velocity and fine motor coordination[12]. Muscle weakness occurs early [12, 27] and the most active muscle groups, usually on dominant side are involved, such as the extensors of the forearms, wrist and fingers [12].

It is hypothesized that lead can interfere with function of neurotransmitter acetylcholine and cellular processes which require calcium. Lead affects mitochondrial oxidative phosphorylation and disturbs the calcium-mediated cellular channels that can influence physiological function in neurons and bone cells. In this study, grip strength was significantly lower in participants in BPb quartiles 2-4 in unadjusted models. However, it did not reach statistical significance when adjusted for other covariates. Clearly more research is needed to assess the complex toxicity of lead on neuromuscular function in older men.

In the current study BPb was not associated with any adverse affect on cognitive function. However, these results are different from our group's earlier studies in elderly women who had a significantly higher risk of falls, and worse neurological performance with increasing BPb [9, 28]. It is not surprising as in men the median BPb assessed in 2007-2008 is 2 μg/ d L compared to women who had higher average BPb, 5.3 μg/ d L in 1990-1991. The decline in mean BPb noticeable over these two studies is reflective of the decreasing mean BPb in the population following regulatory changes limiting leaded gasoline use in the US.

This study has a number of strengths. A well-characterized cohort of community-dwelling older men was studied. A range of cognitive, physical and BMD assessments were completed. Limitations of this study included use of blood lead as the measure of lead exposure. Studies in future should test bone lead as it is a better measure of the cumulative absorbed lead. Further, our results may not be generalizable to non-Caucasian elderly men. Others limitations include this study's inability to establish causality or exclude the presence of residual confounding.

In conclusion, BPb in this study was associated with lower hip BMD. These results as well as other work provide some evidence that blood lead concentrations might impact osteoporosis in older men. Although further work is important to reproduce these findings, it is possible that part of age related bone fragility may be associated with environmental exposures.

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Table 1

Characteristics of MrOS Lead Study Participants, across Blood Lead Quartiles

Characteristics Mean ± sd, or n (%)	N=445	Overall	Blood Lead Concentration (µg/dl) Quartiles				P-value
			1	2	3	4	
			(≤1) N=126	(>1,≤2) N=175	(>2,≤3) N=84	(>3) N=60	
Age (years)	445	79.5±4.9	78.9	79.1	79.5	81.5	.004
Education College or greater vs. high school	445	214 (48)	66 (52)	86 (49)	39 (46)	23 (38)	.336
Body mass index (kg/m2)	445	28.2±4.2	28.8	28.0	28.5	27.9	.657
Current smoking (yes/no)	445	11 (2.5)	0 (0)	7 (4)	3 (3.6)	1 (1.7)	.140
Alcohol (average no of dr /wk)*	444	0.23 (4.3)	0 (2)	0.69(5.0)	0.23(7)	0.23(7)	.015†
BMD (g/cm^2)‡							
Femoral neck	438	0.78±0.13	0.78	0.80	0.76	0.73	.001
Total hip	438	0.95±0.15	0.96	0.98	0.92	0.91	.004
Lumbar Spine	434	1.31±0.32	1.27	1.35	1.28	1.31	.183
Physical Function							
Grip strength (kg)	432	34.8±8.2	35.4	35.9	33.9	31.8	.006
Leg extension power (watts)	329	164.9±53	166.4	169.7	159.7	154.0	.313
Walk speed (m/s)	435	1.02±0.23	1.05	1.04	0.99	0.98	.087
Narrow walk (m/s)	302	1.09±0.24	1.08	1.12	1.07	1.04	.258
Use arms to stand up (yes/no)	445	59 (13)	19 (15)	17 (10)	13 (15)	10 (17)	.350
Cognitive function							
Trails B test score (0-300 sec)§	414	123.2±57	120.7	120.8	122.8	130.0	.330
Teng score 3MS (0 to 100)	442	92.3±0.0	92.5	92.7	92.3	90.7	.247

*Median (interquartile range)

†Wilcoxon non-parametric test

‡Bone Mineral Density

§An increase in this performance measure indicates a decline in cognitive function

Table 2

Age and Multivariate Adjusted Bone Mineral Density (BMD) and Grip strength across Blood Lead Quartiles

	Blood Lead concentration (μg/dl) quartiles				
Characteristics	**Q1**	**Q2**	**Q3**	**Q4**	**p-trend**
Bone Mineral Density					
Femoral neck					
Age adjusted	0.78 (0.74, 0.79)	0.80 (0.78, 0.82)	0.76 (0.73,0.79)	0.74 (0.71,0.77)	<.001
Multivariate adjusted*	0.77 (0.75,0.79)	0.80 (0.78,0.82)	0.76 (0.73,0.79)	0.73 (0.70,0.76)	<.001
Total hip					
Age adjusted	0.96 (0.93, 0.98)	0.97 (0.95,0.99)	0.92 (0.95, 0.99)	0.92 (0.88, 0.96)	<.001
Multivariate adjusted*	0.95 (0.93, 0.98)	0.98 (0.96,0.99)	0.92 (0.89, 0.95)	0.91 (0.88, 0.95)	.004
Grip strength, average of right and left, Kg					
Age adjusted	34.9 (33.6, 36.3)	35.7 (34.5, 36.7)	33.9 (32.3, 35.6)	33.4 (31.4, 35.3)	<.001
Multivariate adjusted*	34.9 (33.6, 36.3)	35.7 (34.6, 36.8)	34.0 (32.4, 35.6)	33.4 (31.5, 35.4)	.148

*Education, smoking, alcohol consumption, body mass index

Table 3

Association of Blood Lead Concentration (log transformed) with multivariate adjusted Lumbar Bone Mineral Density (BMD) and Performance Measures in Linear regression

	β (95% CI)	SE β	p-value	R^2
Bone Mineral Density				
Lumbar Spine				
Age adjusted	0.02 (−0.04,0.08)	0.03	.573	0.01
Multivariate adjusted*	0.03 (−0.03,0.09)	0.03	.362	0.02
Cognitive Function				
Trail making B (s)				
Age adjusted	3.35 (−6.89, 13.58	5.21	.521	0.10
Multivariate adjusted*	2.72 (−7.65, 13.09)	5.27	.606	0.12
Teng score 3MS (0 to 100)				
Age adjusted	−0.19 (−1.30, 0.91)	0.56	.733	0.14
Multivariate adjusted*	−0.01 (−1.10,1.07)	0.55	.984	0.18
Physical Performance				
Leg extension power, watts				
Age adjusted	0.71 (−8.96, 10.4)	4.92	.885	0.27
Multivariate adjusted*	0.13 (−4.23, 4.49)	4.99	.978	0.29
Walk speed, m/s				
Age adjusted	−0.02 (−0.06,0.02)	0.02	.276	0.19
Multivariate adjusted*	−0.02 (−0.06,0.01)	0.02	.238	0.23
Narrow walk, m/s				
Age adjusted	0.01 (−0.05,0.05)	0.02	.985	0.06
Multivariate adjusted*	−0.02 (−0.06, 0.01)	0.02	.238	0.23
Use arms to stand up†	OR (95% CI)	SE	p-value	R^2§
Age adjusted	0.85 (0.50, 1.45)	0.23	.559	0.05
Multivariate adjusted*	0.85 (0.49, 1.47)	0.24	.556	0.07

*Education, smoking, alcohol consumption, body mass index

†Logistic regression

§Pseudo R^2 (Hosmer & Lemeshow), χ^2 (2) =16.28 for age adjusted model and χ^2 (6) =25.01 for multivariate model