Survival Patterns of Lead-Exposed Workers With End-Stage Renal Disease From Adult Blood Lead Epidemiology and Surveillance Program

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Abstract: *Background:* One previous study has shown that patients with end-stage renal disease (ESRD) with higher blood lead levels (BLLs) have shorter survival, in a cohort without occupational exposure where follow-up began an average of 5 years after dialysis (a survivor population). *Methods:* The authors studied individuals with at least 1 blood lead test who were part of an occupational lead surveillance program sponsored by the National Institute for Occupational Safety and Health and were diagnosed with ESRD. The authors studied the effect of BLL on survival from time of ESRD diagnosis after adjusting for potential confounders. Cox proportional hazards models were run, in which death was the end point and follow-up time was the time variable. *Results:* There were 434 ESRD cases with 82% males, 65% white and 31% African American; 51% had 1 blood test, whereas the remainder had a median of 5 tests. The median years of follow-up were 2.7 years with 219 deaths in the cohort. After adjusting for covariates (eg, transplantation status, age at diagnosis, glomerular filtration rate, comorbidities and ethnicity), the authors found no significant association between highest measured BLL and mortality across categories; 0 to <5 μg/dL (hazard ratio [HR] = 1.00), 5 to <25 μg/dL (HR = 1.09; 95% confidence interval [CI]: 0.70–1.70), 25 to <40 μg/dL (HR = 1.28; 95% CI: 0.81–2.02), 40 to <50 μg/dL (HR = 0.89; 95% CI: 0.48–1.63) and 50+ μg/dL (HR = 1.09; 95% CI: 0.66–1.81). *Conclusions:* The authors found no association between BLL and survival after ESRD diagnosis. The authors' finding differs from earlier findings, possibly because the cohort had higher blood leads (25 versus 10 μg/dL), follow-up began at the time of ESRD diagnosis, and BLLs were measured before ESRD incidence.

Key Indexing Terms: Adult Blood Lead Surveillance; Blood lead level; End-stage renal disease; Mortality; Occupational exposure. **[Am J Med Sci 2015;349(3):222–227.]**

Lead is neurotoxic in children and can cause acute poisoning in adults. Adult chronic lead exposure has been associated with kidney dysfunction and higher incidence of, and mortality from, nonmalignant kidney disease. With the U.S. Environmental Protection Agency's establishment of permissible level of lead in the air[1] and subsequent reduction of lead use in commercially available products (particularly leaded gasoline), ambient lead exposure has been greatly reduced in the United States. Nonetheless, there continues to be substantial occupational exposure to lead. The National Institute of Occupational Safety and Health (NIOSH) estimated that more than 3 million workers in the United States were potentially exposed to lead at work in the 1980s.[2,3] More recent estimates can be made using data from NIOSH's Adult Blood Lead Surveillance (ABLES) program; data from 37 states indicated that approximately 130,000 workers had been tested for blood lead in 2005.[4]

A recent (2006) comprehensive review of lead-related nephrotoxicity concluded that lead contributes to nephrotoxicity, even at blood lead levels (BLLs) below 5 μg/dL, especially in people with other illnesses such as hypertension and diabetes.[5] There is evidence of BLLs being associated with all-cause and cardiovascular-cause mortality in the general population.[6–8] Risk factors of mortality in patients with end-stage renal disease (ESRD) have been studied in depth. Cardiovascular disease was established early on as the main cause of death[9]; subsequent research has pointed to diverse factors such as protein malnutrition and hypoalbuminemia,[10] hemoglobin variability[11] and altered calcium/phosphorus metabolism[12] as predictors of mortality in patients with ESRD. However, to date, very few studies have considered BLL as a risk factor associated with survival/mortality among incident ESRD cases developing after exposure to lead. Although there are studies among the general population looking at survival after diagnosis of ESRD,[13,14] few have considered blood lead as a risk factor. In a study of patients undergoing chronic peritoneal dialysis, Lin et al[15] have demonstrated an association between BLLs and all-cause 18-month mortality. In previous work, the authors found evidence suggesting association between lead exposure and ESRD[16] and lead exposure and subsequent mortality.[17] The present research aims to explore whether blood lead, as measured before ESRD developed, was associated with worse survival after ESRD in occupationally exposed lead workers after adjusting for other variables.

METHODS

Data Sources/Study Participants

The ABLES program, sponsored by NIOSH, has collected state-level data on blood lead exposure since 1987.[18] In participating states, state agencies collected data on all subjects tested in any laboratory in the state doing blood lead tests. NIOSH has collected data on industry for a limited number of ABLES subjects (n = 6,999).[19] Of these, 62% were in manufacturing, 10% in construction, 7% in metal mining, 1% in trade (scrap and waste materials) and 20% were in other industries or data were unavailable.

The authors categorized each blood lead test into 1 of 5 categories namely <5, 5 to <25, 25 to <40, 40 to <50 and

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50+ μg/dL or categories 1 through 5, respectively. Categories <25, 25 to 40 and 40+ have been traditionally used to categorize occupational blood leads, whereas the lowest category 5 μg/dL essentially was equivalent to nonoccupational U.S. BLLs. The authors subdivided the highest category at 50 μg/dL, which is the OSHA (Occupational Safety and Health Administration, U.S. Department of Labor) cutoff for removing subjects from lead exposure in construction until their BLL drops below 40 μg/dL. The authors then assigned a final single blood lead category for each subject, defined as the highest category ever achieved by an individual. In the full cohort and in the present data set, the authors found that the blood levels for the majority of subjects with multiple tests were generally in the same blood lead category.[17] In the current subset, 50.7% had only a single measurement. Overall the authors found 89.6% of the current study population stayed in the same (65.44%) or changed only 1 category. Among those individuals with multiple observations (n = 214), 78.97% stayed in the same (29.91%) or changed only 1 category. Hence the highest category achieved in many cases was the same as their category based on their average or median BLL.

The authors obtained data from 11 state ABLES programs —Connecticut, California, Ohio, Minnesota, Iowa, Pennsylvania, New York, New Jersey, Wisconsin, Michigan and Massachusetts from their year of first participation until 2008. The authors excluded everyone who was tested after 2005 to avoid very short follow-up time. The authors also excluded any subject missing information on date of birth, test date or BLLs and observations with BLL greater than 250 μg/dL as these values were considered implausible. The authors further excluded all people who were tested for the first time after the age of 70 years or before the age of 18 years as these were more likely to be acute exposures and hence unlikely to be occupational exposures; the authors wished to analyze an occupationally exposed cohort. However, before the authors had applied the last of these criteria, an early data set had been sent to United States Renal Data System (USRDS) with data from 6 states—California, Connecticut, New Jersey, Iowa, Ohio and Michigan. In this earlier data set, there were approximately 12,000 people who were not a part of the new resampled cohort. The authors decided to include these 12,000 people in the current analysis, as long as they fulfilled the age criteria above (there were 100 ESRD cases in this group). The authors included these 100 cases for this article.

The authors first selected everyone from the states who had ever had a BLL reading in categories 3 or 4 or 5. The authors then selected an equal number of people from categories 1 and 2 (50% from each category) stratified by state. The authors then matched this cohort against the NDI (National Death Index) to obtain vital status information and USRDS to determine who had developed incident ESRD after having been previously tested for blood lead. The last 3 states (Wisconsin Michigan and Massachusetts) opted to do their own data processing and matching with the NDI and USRDS. They followed the same selection pattern but independently submitted data to NDI and USRDS and sent us de-identified data.

The authors used name, date of birth, gender, race (when available) and Social Security Number (SSN; when available) for matching with the NDI and USRDS databases until the end of 2010. Similar matching of other occupational cohorts with USRDS for renal disease incidence has been done in the past.[20,21]

Follow-up of the cohort for renal disease incidence, through matching with the USRDS, and for vital status through NDI, was through 2010; for 3 states which did their own matching and sent us de-identified data (~15% of the cohort, Wisconsin, Massachusetts and Michigan), follow-up went through 2009.

To determine whether a match with the NDI was a true match from among the multiple matches reported by NDI, the authors only selected those who were assigned a status code of 1 by NDI, indicating a high probability of a match. If person's last blood lead date was after their date of death, then the match was false and the authors dropped all information received from NDI, that is, these subjects were considered alive. If there were multiple matches with status code 1, the authors selected the one the NDI reported as an exact match. If there was no exact match, the authors sorted all the status codes = 1 by probability score. If highest probability score was ≥40 and state of death was same as state where a subject was tested, then the authors selected that observation. If there were more than 1 match meeting this criterion, then the authors selected the 1 with the higher probability score of match. If the authors were unable to select a match based on the above criteria, the authors dropped those observations entirely from the final data set to avoid misclassification of outcome.

Regarding USRDS, anyone whom USRDS considered a match was accepted and was considered to be an ESRD case. Of these cases, 137 had been diagnosed with ESRD before their first blood lead test date and were excluded, and hence, the authors were left with 434 unique ESRD cases for this study. The authors also obtained data on date of death and cause of death for ESRD cases from the USRDS, as the USRDS follows all ESRD cases longitudinally. If an ESRD case was not declared dead by NDI but had been reported as dead by the USRDS, the authors considered the person to be dead. The USRDS uses the Social Security Administration to determine deaths. In addition to standard list of matching variables, the authors also requested the USRDS to provide detailed information on the following Core Standard Analysis Files data-Treatment History (RXHIST), Medical Evidence (MEDEVID95), Medical Evidence (MEDEVID05), Death information (DEATH), Transplant (TX) and patient information (Patients). These data sets provided us with information on glomerular filtration rate (GFR) at the time of ESRD diagnosis, body mass index (BMI), race, comorbidity, transplant status, type of medical insurance and Spanish ethnicity. All of these were considered potential confounders of a possible association between lead exposure and mortality. However, comorbidity could also be an intermediate variable as opposed to a potential confounder.

The authors used Cox proportional hazard models to evaluate association of survival pattern and lead exposure level in 5 aforementioned categories among ESRD cases after adjusting for covariates, including, race, gender, ethnicity, ever transplanted, GFR before start of dialysis, BMI, age at ESRD diagnosis, insurance status, year of ESRD diagnosis (for cohort effect), cause of ESRD and comorbidities, specifically chronic obstructive pulmonary disease and any cardiac disease. Other variables were not included in the model, as they were not associated with mortality at the $P = 0.10$ level in univariate analyses. GFR and age at ESRD diagnosis were modeled as continuous variables, as they showed a monotonic trend when examined in quartiles and quintiles, respectively. BMI was divided into 4 categories—underweight (<18.5 kg/m^2), normal (18.5 to <24.9 kg/m^2), overweight (24.9 to <30 kg/m^2) and obese (≥30 kg/m^2).

The authors used backward elimination to reduce the full model to final models using Akaike Information Criteria and P values (variables with P values >0.1 were dropped). Lead exposure, the key variable of *a priori* interest, was retained in all models.