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RESEARCH LETTER

Association of environmental lead toxicity and hematologic outcomes in patients with advanced kidney disease

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Despite regulatory advances over the past two decades, low levels of environmental heavy metal contamination remain widespread. Because lead is predominantly excreted by the kidney, patients with chronic kidney disease (CKD) may be particularly susceptible to lead toxicity. We have recently used regulatory data to demonstrate associations between higher levels of lead exposure in community drinking water and lower hemoglobin concentrations and higher erythropoietin stimulating agent (ESA) utilization among those with end-stage kidney disease (ESKD) [1]. To further investigate these findings, we used portable X-ray fluorescence (XRF) to measure levels of tibial lead in 69 patients seen for routine nephrology care. Tibial lead is widely regarded to reflect total lead accumulation [2]. While standard K-shell fluorescence remains the standard for measuring bone lead, recent advances in portable XRF techniques offer a more clinically feasible methodology which is under clinical evaluation [3–6]. We compared tibial lead levels to hemoglobin concentrations taken at the time of the clinic visit. Gender-specific thresholds [<11.2 g/dL (women) and 13.7 g/dL (men)] were used to define anemia. We hypothesized that tibial lead levels would be indirectly associated with hemoglobin concentrations, particularly for those with more severe CKD, among whom the myelosuppressive effects of lead would be synergized by the decreased erythropoietin functionality that accompanies anemia of CKD.

We used multivariate linear and logistic regression to examine the association of tibial lead with hemoglobin concentrations and odds of anemia, respectively, adjusted for age, gender and ethnicity, and explored for effect modification by cohort median estimated glomerular filtration (eGFR) (43 mL/min/1.73 m²). The 2021 CKD Epidemiology Collaboration equation was used to generate race-free estimates of glomerular filtration. In addition, we described the associations of tibial lead with iron concentrations, % transferrin saturation and ferritin among individuals with available laboratory data. As a model control, we examined whether tibial measures of copper, a heavy metal predominantly metabolized by the liver, was associated with hemoglobin concentrations.

The average patient age was 68.2 (8.4) years; 36% ($n = 25$) were female and 17% ($n = 12$) were African American. Large proportions of patients had hypertension (83%, $n = 56$) and diabetes (44%, $n = 29$). The mean values for eGFR and hemoglobin were 42 (4.3) mL/min/1.73 m² and 12.6 (2.2) g/dL, respectively. Tibial lead levels did not relate to renal function (correlation –0.06; $P = .60$). When stratified by median cohort tibial lead level (5.1 μg/g), those with higher levels of tibial lead had lower hemoglobin concentrations [12.3 (2.6) versus 12.9 (1.7) g/dL; $P = .31$] and higher proportions of anemia [50% ($n = 17$) vs 34% ($n = 12$); $P = .20$], respectively.

Among those with eGFR below the cohort median of 43 mL/min/1.73 m², among whom hemoglobin concentrations were lower [11.1 (1.9) vs 13.3 (2.1) g/dL; ($P < .001$)] and anemia proportions were higher [58% ($n = 20$) vs 25% ($n = 9$)], tibial lead was associated with lower hemoglobin concentrations and higher proportions of anemia (Fig. 1). In adjusted analyses, the associations between tibial lead and hemoglobin concentrations and anemia proportions were both significantly more robust in those with lower eGFR (multiplicative interaction between continuous measures of tibial lead and eGFR P-values .04 for hemoglobin and .01 for anemia, respectively). In those with eGFR below 43 mL/min/1.73 m², a 1 μg/g higher tibial lead concentration was associated with a 0.12 g/dL (–0.21, –0.02) lower hemoglobin concentration and a 23% (1.03, 1.47) higher odds of anemia. Tibial lead did not meaningfully associate with hemoglobin or anemia among those with eGFR ≥43 mL/min/1.73 m². Tibial lead was not meaningfully associated with measures of iron deficiency. Log transformation of data and correction for ESA use resulted in similar findings. Tibial levels of copper did not associate with hemoglobin concentrations or odds of anemia, and were not modified by eGFR.

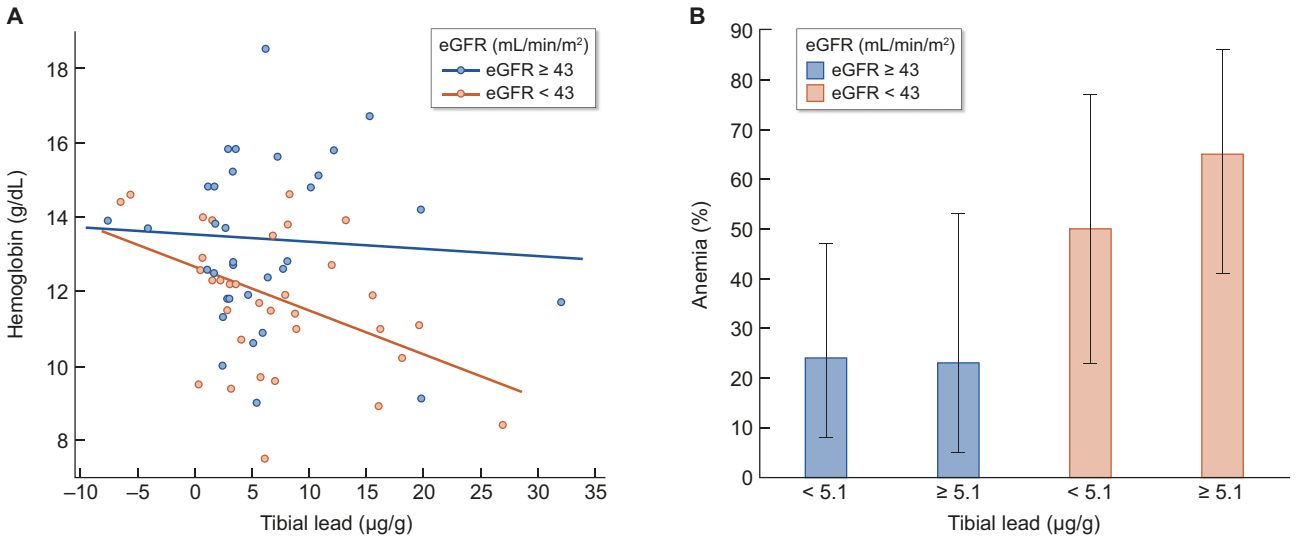

Figure 1: Association of tibial lead levels with hematologic outcomes according to CKD severity. Univariate change in hemoglobin concentration per 1 μg/g higher tibial lead concentration, and proportions with anemia according to cohort median tibial lead concentration, stratified by CKD severity. Multiplicative interaction *P*-values between tibial lead and eGFR were .04 and .01 for hemoglobin and anemia, respectively.

Our findings suggest that among patients with advanced CKD, environmental lead exposure is associated with a higher risk of anemia and lower hemoglobin concentrations. The effect modification observed in our analysis is consistent with a synergistic effect of lead toxicity in those already susceptible to myelosuppression due to CKD. Accumulating in the proximal tubule, the site of erythropoietin production, lead inhibits erythropoietin production [7–9], which is already compromised in CKD. Furthermore, lead inhibits heme synthesis and decreases erythrocyte survival [10, 11], which are similarly affected by uremia [12]. Accordingly, that the associations between tibial lead and myelosuppression are most robust in those with advanced CKD adds biologic plausibility and specificity to our findings, and suggests that even low levels of lead exposure, as found commonly in our environment, may have important clinical consequence for those with CKD.

Whether tibial lead will associate with other lead-related adverse outcomes warrants study. In particular, given that lead toxicity has been associated with cognitive decline [13, 14], which is a highly prevalent condition in CKD [15], a putative role of lead in CKD-related cognitive dysfunction needs to be examined. Limitations of our study included its relatively small size, which precluded further stratification by renal function and limited the analytic power. In addition, we did not have measures of circulating lead, nor could we fully account for lead exposure, limiting conclusions about whether renal function modifies the risk to any given exposure.

In summary, for individuals with CKD, environmental lead exposure may be a meaningful and preventable determinant of anemia. Whether tissue lead levels associate with other lead-related diseases will require further study.

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CONFLICT OF INTEREST STATEMENT

None declared.

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