Kidney360

Levels of Lead in Residential Drinking Water and Iron Deficiency among Patients with End Stage Kidney Disease

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Key Points

- Low levels of drinking water lead contamination are associated with an increased risk of iron deficiency among those with kidney disease.
- Black people seem particularly susceptible to the association of lead contamination and iron deficiency.

Abstract

Background Although those with kidney disease may have heightened susceptibility to heavy metal toxicity, whether low levels of drinking water lead contamination have clinical consequence is unknown.

Methods Given that lead toxicity is known to associate with iron deficiency, we merged data from the Environmental Protection Agency (EPA) Safe Drinking Water Information and United States Renal Data Systems to examine whether municipal 90th percentile drinking water lead levels associate with iron deficiency among incident dialysis patients. Iron deficiency was defined across thresholds of transferrin saturation (<10% and 20%) and ferritin (<100 and <200 ng/ml), and simultaneous transferrin saturation <20% and ferritin <200 ng/ml, all obtained within 30 days of dialysis initiation. The average 90th percentile of drinking water lead samples per patient city of residence over a 5-year period before dialysis initiation was examined at the <1 μg/L level of detection, and at the 25th, 50th, and 100th percentile of the EPA's actionable level (15 μg/L).

Results Among 143,754 incident ESKD patients, those in cities with drinking water lead contamination had 1.06 (95% CI, 1.03 to 1.09), 1.06 (95% CI, 1.02 to 1.10), and 1.07 (95% CI, 1.03 to 1.11) higher adjusted odds of a transferrin saturation <20%, ferritin <200 ng/ml, and simultaneous transferrin saturation <20% and ferritin <200 ng/ml, respectively. These associations were apparent across the range of lead levels found commonly in the United States and were significantly greater among Black patients (multiplicative interaction *P* values between lead and race <0.05).

Conclusions Even exposure to low levels of lead contamination, as commonly found in US drinking water, may have adverse hematologic consequence in patients with advanced kidney disease. These associations are particularly evident among Black people and, although consistent with other environmental injustices facing minorities in the United States, might reflect a greater susceptibility to lead intoxication.

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Introduction

Iron deficiency affects large proportions of the population worldwide, and has a range of pathophysiologic consequences, including anemia, fatigue, restless legs, and malaise. It occurs with particular frequency in CKD, where it is an important determinant of erythropoietin stimulating agent (ESA) use and overall health care utilization.

Lead toxicity is an important environmental determinant of iron deficiency. Although lead exposure most typically occurs from workplace contact, particulate inhalation, and paint ingestion, contamination of drinking water is an increasingly recognized source (1–9). The aging infrastructure of water delivery systems in the United States, including lead service lines and household plumbing, are susceptible to leaching, as most dramatically evidenced in Flint, Michigan (10). The Environmental Protection Agency (EPA) recognizes no safe limit of lead exposure and, although establishing a maximum contaminant goal level of zero, mandates regulatory action only when the 90th percentile of tested samples exceeds 15 μg/L. Accordingly, significant variability in lead contamination remains in US drinking water.

Recently, we showed that low levels of lead exposure, as found widely in drinking water systems across the United States, are associated with lower levels of hemoglobin and higher rates of ESA

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utilization among incident ESKD patients (11). To examine the potential hematologic consequences of lead exposure in this highly susceptible population further, herein we examine the association of drinking water lead levels and iron deficiency. In addition, given that Black people have higher rates of iron deficiency (12) and anemia (13,14) and, simultaneously, higher rates of lead exposure than other racial/ethnic groupings (15), we examine these associations across racial strata.

Materials and Methods

Using data from the United States Renal Data System (USRDS), the national registry of patients with ESKD, we identified all patients who initiated dialysis between 2012 and 2017 (16). For each patient, we identified the city of residence, which was defined by a single ZIP code for ≥6 months preceding dialysis initiation. We used data from the ESKD Medical Evidence Report, a standardized form that the Centers for Medicare and Medicaid Services (CMS) required for the registration of all incident ESKD patients, to ascertain demographic information, comorbidities, pre-ESKD laboratory measurements, including serum creatinine and hemoglobin, and pre-ESKD ESA use. We used data in CROWNWeb, a CMS data management system that all Medicare-certified dialysis facilities use to supply laboratory information from the first month of dialysis therapy. CROWNWeb began to accept data in June 2012. As previously described (11), we used the Safe Drinking Water Information System (SDWIS) Federal Data Warehouse to describe concentrations of lead in city drinking water systems. We joined the USRDS and SDWIS datasets by city and state to create a complete dataset of 187,298 incident ESKD patients. Of these, 143,754 patients in 7349 cities had reported iron studies during the first month of dialysis, comprising the primary dataset.

Federal guidelines mandate representative lead sampling on the basis of the size of each water system and its previous lead concentrations, ranging from 5 to 100 samples per water system, over a 6-month to 3-year interval (17). If ≥10% of these samples exceed the EPA's actionable level of 15 μg/L, the municipal utility system must take corrective action and increase the frequency of testing. The 90th percentile of all results are cataloged in the SDIWS according to the dates of water surveillance. We generated an annual lead level for each water system by matching the lead results to each year within the sampling period. Because of repeated measures per surveillance period, we averaged the maximum reported lead level per year of all water systems serving a city, weighted by the number of individuals served by each water system, to derive an annual city-wide lead level. For each patient, we calculated the average of city-wide levels during the 5 years preceding dialysis initiation. Given that the 90th percentile threshold may not accurately quantify the exposure at the end-user level, we compared patients in cities with any detectable drinking water lead (≥1 μg/L) to those with undetectable levels, and also categorized the exposure by percentiles (25th, 50th, and 100th) of the EPA's current actionable level (15 μg/L).

Given the complexity of iron metabolism and multiple definitions of iron deficiency, we explored several primary outcomes, including transferrin saturation <10% and <20%, ferritin <100 and <200 ng/ml, and simultaneous transferrin saturation <20% and ferritin <200 ng/ml. Patient characteristics included age, sex, race (White, Black, Asian, other/unknown), diabetes mellitus, heart failure, hypertension, tobacco use, eGFR (as calculated by the Modification in Diet in Renal Disease four-factor equation), and year of dialysis initiation. Median household income and unemployment rate were ascertained at the ZIP code level using data from the United States Census American Community Survey 5-year estimates.

We summarized patient characteristics according to categories of drinking water lead concentrations. We used logistic regression, including all patient characteristics and socioeconomic factors, to examine the adjusted association of city-wide lead levels with thresholds of iron deficiency. Exposure was examined at the level of detection (90th percentile lead level ≥1 μg/L) and across EPA thresholds.

We explored the significance of multiplicative interactions between race (Black versus non-Black, excluding those with missing race categorization) and detectable drinking water lead and provide the stratified results. We also explored whether results differed according to pre-ESKD ESA use or nephrology care, hemoglobin concentrations (pre-ESKD), and household income. Institutional Review Board permission was obtained for research activities (BIDMC protocol 2020P000200).

Results

Among patients initiating dialysis in the United States from 2012 to 2017, 80% (n=114,696) lived in cities with measurable (≥1 μg/L) 90th percentile lead levels in municipal drinking water. Demographics, comorbidities, and socioeconomic factors were similar across categories of drinking water lead exposure (Table 1), except for higher proportions of Black patients and patients with heart failure in cities with higher drinking water lead.

Iron deficiency was more common among ESKD patients residing in cities with lead-containing drinking water, particularly among Black people (Figure 1). In models that adjusted for a range of individual and environmental factors (Table 2), detectable levels of drinking water lead were associated with 1.06 (95% CI, 1.03 to 1.09) higher odds of transferrin saturation <20%, 1.06 (95% CI, 1.02 to 1.10) odds of ferritin <200 ng/ml, and 1.07 (95% CI, 1.03 to 1.11) odds of simultaneous transferrin saturation <20% and ferritin <200 ng/ml. These associations were significantly more robust among Black patients (Table 3).

There was no effect modification by ESA utilization or nephrology care before ESKD onset, pre-ESKD hemoglobin concentration, or household income (multiplicative interaction P values all >0.05).

Discussion

Among patients starting dialysis in the United States from 2012 to 2017, those living in cities with measurable amounts of lead in their residential drinking water had a higher prevalence of iron deficiency as estimated from iron, transferrin, and ferritin levels. These associations were

Table 1. Baseline characteristics according to 90th percentile levels of lead in residential drinking water

Characteristic	Lead in Drinking Water, μg/L				
	<1	1 to <3.75	3.75 to <7.5	7.5 to <15	≥15
Number of patients	28,178	63,765	33,584	15,639	2588
Number of cities	1903	4183	2522	857	254
Pre-ESKD patient characteristics					
Age, yr	63 (14.9)	63.4 (15.4)	63.5 (15.6)	63.7 (15.6)	62.9 (15)
Women	42	42	42	42	42
Race					
White	65	68	74	66	63
Black	25	27	22	29	35
Asian	8	4	3	4	2
Other/unknown	3	2	1	1	1
Comorbidities					
Diabetes	60	58	59	57	57
Hypertension	89	89	89	89	89
Congestive heart failure	27	28	30	31	31
Tobacco use	6	7	6	6	6
Body mass index	29.9 (8)	29.8 (7.9)	29.6 (7.9)	29.4 (8)	30.1 (8.1)
eGFR, ml/min per m^2	9.8 (4.5)	10.2 (4.5)	10.1 (4.5)	10 (4.6)	9.8 (4.5)
Peritoneal dialysis	6	5	4	4	5
Nephrology care[a]	78	77	74	76	77
Pre-ESKD ESA use[b]	23	22	23	24	24
Laboratory values, %					
Transferrin saturation	23.4 (10.6)	23 (10.4)	23.1 (10.5)	23.2 (10.7)	22.7 (10.1)
Transferrin saturation <10%	4	4.2	4.2	4.2	4.4
Transferrin saturation <20%	40.4	42.3	41.6	41.9	42.7
Ferritin	447 (382)	443 (385)	447 (388)	460 (396)	436 (370)
Ferritin <100 ng/ml	10.1	10.7	10.8	9.7	10.8
Ferritin <200 ng/ml	27.8	28.9	28.6	27.2	29.2
Transferrin saturation <20% and ferritin <200 ng/ml	12.9	14	13.4	13	14.3
Zip code characteristics					
Median household income, $1000K	55.81 (20.9)	54.3 (21.2)	50.9 (23.4)	53.4 (25.2)	52.3 (22.3)
Unemployment rate	7.8 (3.5)	7.9 (4)	8.8 (5.4)	8.9 (4.8)	8.6 (4.7)

ESA, erythropoietin stimulating agent.
[a]Missing in 16,109.
[b]Missing in 40,941.

observed at levels of drinking water lead well below the EPA's current actionable level that mandates water remediation and were particularly apparent among Black people.

Although there is extensive epidemiologic evidence linking iron deficiency and lead toxicity (18–21), the complexity of iron metabolism renders pathophysiologic explanations speculative. Heavy metals absorption occurs competitively across the gastrointestinal tract, and iron supplementation may minimize the toxicity of environmental lead exposure (20,22). The binding of hepcidin to ferroportin on the membranes of iron-exporting cells, including enterocytes, induces endocytosis and proteolysis of ferroportin, thereby reducing iron delivery to plasma. Although there are known determinants of hepcidin activity, including inflammation, iron, and erythropoietin, whether it is modulated by lead has not been examined (23). Polymorphisms in a range of iron metabolism mediators have been linked to differences in lead susceptibility (24–27).

Explanations for the significantly larger associations between drinking water lead levels and iron deficiency in Black than White patients are similarly hypothesis generating. Ongoing socioeconomic inequities likely contribute to differences in exposure (28). Additional environmental toxins that associate with drinking water contamination, not accounted for in our analysis, may confound our findings. In addition, given the nonrandom sampling of water systems, 90th percentile values likely misclassify individual levels of exposure, particularly for those most vulnerable to lead contamination (29,30). Such systematic underestimation of environmental lead and its negative effects is particularly concerning for Black people, among whom socioeconomic disadvantage increases vulnerability, and higher rates of kidney disease increase susceptibility, to lead toxicity (5,31,32). Whether unrecognized lead toxicity may contribute to the higher rates of anemia and ESA utilization among Black people than other ethnic groupings requires further study (33,34). Finally, the role of genetic variations in iron and lead metabolism requires further study.

Our findings further highlight the heightened susceptibility to environmental toxins among patients with kidney disease (35). Although most individuals absorb only a small fraction of ingested lead, mitigating the toxicity of water contamination, unique pathophysiologic complications of CKD, including hypocalcemia, vitamin D deficiency (36,37), and low protein diets (38), increase the

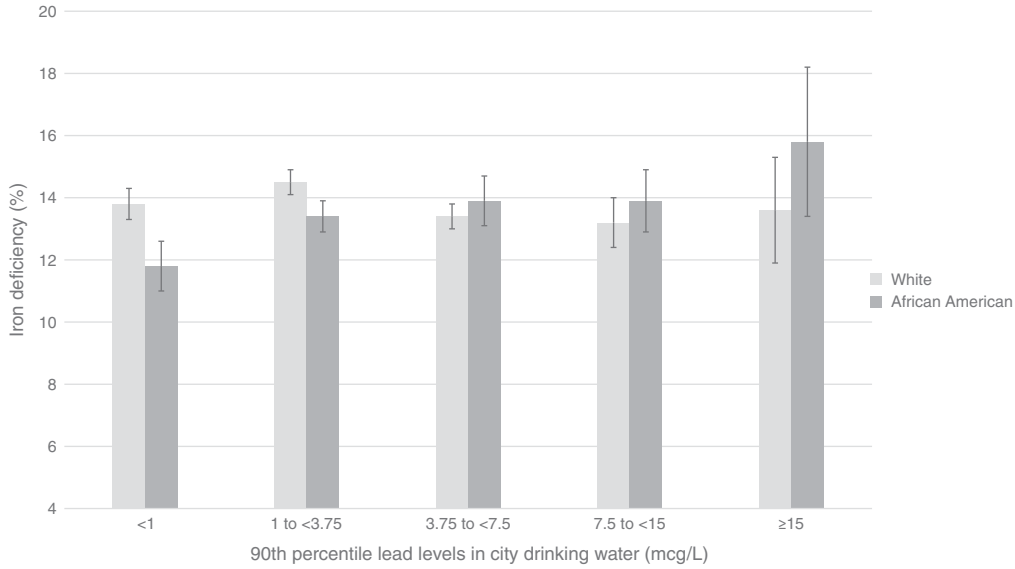

Figure 1. | Proportions of Black and White ESKD patients in the United States with iron deficiency, as defined by a transferrin saturation <20% and ferritin <200, according to 90th percentiles of lead in municipal drinking water. Compared with undetectable levels of lead, residence in cities with higher lead levels was associated with significantly higher unadjusted risk of iron deficiency among Black patients ($P<0.001$) but not among White patients.

proportion of lead absorbed across the gastrointestinal tract. Furthermore, because excretion of lead primarily occurs through glomerular filtration, patients with CKD are particularly susceptible to lead accumulation and, accordingly, have circulating blood levels several fold higher than those with normal function (39,40).

Our study has several important limitations. Without individual patient dietary practices, including use of tap versus bottled water, direct assay of water lead content, and residential stability, lead exposure cannot be accurately adjudicated. Further studies with direct measurement of household water are needed. Although we could not accurately characterize determinants likely to affect iron metabolism, including iron supplementation, underlying inflammation, nutrition, and a range of other disease states, the overall levels of comorbidity burden, pre-ESKD care, and ESA use were generally similar across strata of lead exposure. In addition, given no standard definition of iron deficiency in patients with kidney disease and competing pathophysiologic forces that modify iron storage and handling, misclassification is possible.

In conclusion, for patients with advanced kidney disease, especially Black people, even low levels of lead contamination may have hematologic consequence. Further studies with more precise quantification of lead exposure and body measures of lead accumulation are needed to understand the importance of environmental lead.

Table 2. Adjusted association of residential water systems lead concentration and iron deficiency among patients starting dialysis between 2012 and 2017 in the United States

	90th Percentile Lead Levels in City Drinking Water Systems					
	Thresholds of EPA's Maximum Allowable Drinking Water Lead Content					Detectable Lead
Iron Deficiency	<1 μg/L	1 to <3.75 μg/L	3.75 to <7.5 μg/L	7.5 to <15 μg/L	≥15 μg/L	≥1 μg/L
Transferrin saturation <10%	Ref.	1.02 (0.95 to 1.09)	1.01 (0.93 to 1.1)	1.02 (0.92 to 1.12)	1.08 (0.89 to 1.31)	1.03 (0.96 to 1.1)
Transferrin saturation <20%	Ref.	1.07 (1.04 to 1.1)	1.04 (1 to 1.07)	1.05 (1.01 to 1.09)	1.09 (1 to 1.17)	1.06 (1.03 to 1.09)
Ferritin <100 ng/ml	Ref.	1.07 (1.01 to 1.13)	1.09 (1.02 to 1.16)	0.97 (0.89 to 1.04)	1.08 (0.93 to 1.26)	1.06 (1.01 to 1.11)
Ferritin <200 ng/ml	Ref.	1.07 (1.03 to 1.11)	1.07 (1.02 to 1.12)	0.99 (0.94 to 1.05)	1.09 (0.99 to 1.21)	1.06 (1.02 to 1.1)
Transferrin saturation <20% and ferritin <200 ng/ml	Ref.	1.1 (1.05 to 1.14)	1.04 (0.99 to 1.09)	1.01 (0.95 to 1.08)	1.12 (0.99 to 1.26)	1.07 (1.03 to 1.11)

Data shown as odds ratio (95% confidence intervals). Adjusted for age, sex, race, comorbidities, eGFR, median household income and unemployment rate of patient's zip code of residence, and year of dialysis initiation. EPA, Environmental Protection Agency.

Table 3. Adjusted association of residential water systems lead concentrations and iron deficiency among patients starting dialysis between 2012 and 2017 in the United States

		90th Percentile Lead Levels in City Drinking Water Systems						
		Thresholds of EPA's Maximum Allowable Drinking Water Lead Content					Detectable Lead	
Iron Deficiency	Race	<1 μg/L	1 to <3.75 μg/L	3.75 to <7.5 μg/L	7.5 to <15 μg/L	≥15 μg/L	≥1 μg/L	*P* Value[a]
Transferrin saturation <10%	White	Ref.	1.02 (0.93 to 1.11)	1 (0.91 to 1.1)	1 (0.89 to 1.13)	0.92 (0.71 to 1.19)	1.01 (0.93 to 1.09)	0.63
	Black	Ref.	1 (0.86 to 1.16)	1.07 (0.91 to 1.27)	1.08 (0.89 to 1.31)	1.41 (1.02 to 1.94)	1.04 (0.91 to 1.19)	
Transferrin saturation <20%	White	Ref.	1.06 (1.03 to 1.10)	1.02 (0.98 to 1.06)	1.01 (0.96 to 1.06)	0.99 (0.88 to 1.09)	1.04 (1.01 to 1.08)	0.03
	Black	Ref.	1.1 (1.04 to 1.16)	1.08 (1.01 to 1.16)	1.16 (1.07 to 1.25)	1.28 (1.1 to 1.46)	1.11 (1.05 to 1.17)	
Ferritin <100 ng/ml	White	Ref.	1.03 (0.95 to 1.10)	1.02 (0.95 to 1.1)	0.89 (0.81 to 0.98)	0.99 (0.82 to 1.2)	1.01 (0.95 to 1.07)	0.02
	Black	Ref.	1.16 (1.03 to 1.29)	1.21 (1.06 to 1.38)	1.17 (1 to 1.36)	1.34 (1.04 to 1.72)	1.18 (1.06 to 1.31)	
Ferritin <200 ng/ml	White	Ref.	1.04 (0.99 to 1.09)	0.98 (0.94 to 1.03)	0.92 (0.86 to 0.97)	1.04 (0.91 to 1.18)	1.01 (0.96 to 1.05)	0.001
	Black	Ref.	1.11 (1.03 to 1.2)	1.19 (1.08 to 1.3)	1.16 (1.04 to 1.28)	1.19 (1 to 1.42)	1.14 (1.06 to 1.22)	
Transferrin saturation <20% and ferritin <200 ng/ml	White	Ref.	1.06 (1 to 1.12)	0.98 (0.92 to 1.03)	0.95 (0.88 to 1.03)	0.99 (0.84 to 1.16)	1.02 (0.97 to 1.07)	0.01
	Black	Ref.	1.14 (1.04 to 1.24)	1.19 (1.03 to 1.31)	1.16 (1.03 to 1.31)	1.36 (1.11 to 1.66)	1.16 (1.07 to 1.27)	

Data shown as odds ratios (95% confidence intervals). Adjusted for age, sex, comorbidities, eGFR, median household income and unemployment rate of patient's zip code of residence, and year of dialysis initiation. EPA, Environmental Protection Agency.

[a]Multiplicative interaction term *P* value testing Black versus other racial groupings and lead ≥1 μg/L.

Disclosures

J. Danziger reports consultancy for Healthmap Solutions; ownership interest in Healthmap Solutions; and is the regional medical director at Healthmap Solutions. K.J. Mukamal reports other interests or relationships with US Highbush Blueberry Council and Wolters Kluwer.

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Author Contributions

J. Danziger was responsible for conceptualization, data curation, formal analysis, investigation, and methodology, and wrote the original draft of the manuscript; and both authors reviewed and edited the manuscript.

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