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Plasma Lead Concentration and Risk of Late Kidney Allograft Failure: Findings From the TransplantLines Biobank and Cohort Studies

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Rationale & Objective: Heavy metals are known to induce kidney damage, and recent studies have linked minor exposures to cadmium and arsenic with increased risk of kidney allograft failure, yet the potential association of lead with late graft failure in kidney transplant recipients (KTRs) remains unknown.

Study Design: Prospective cohort study in The Netherlands.

Setting & Participants: We studied outpatient KTRs (n = 670) with a functioning graft for ≥1 year recruited at a university setting (2008-2011) and followed for a median of 4.9 (interquartile range, 3.4-5.5) years. Additionally, patients with chronic kidney disease (n = 46) enrolled in the ongoing TransplantLines Cohort and Biobank Study (2016-2017, ClinicalTrials.gov identifier NCT03272841) were studied at admission for transplant and at 3, 6, 12, and 24 months after transplant.

Exposure: Plasma lead concentration was $\log_2$-transformed to estimate the association with outcomes per doubling of plasma lead concentration and also considered categorically as tertiles of lead distribution.

Outcome: Kidney graft failure (restart of dialysis or repeat transplant) with the competing event of death with a functioning graft.

Analytical Approach: Multivariable-adjusted cause-specific hazards models in which follow-up of KTRs who died with a functioning graft was censored.

Results: Median baseline plasma lead concentration was 0.31 (interquartile range, 0.22-0.45) μg/L among all KTRs. During follow-up, 78 (12%) KTRs experienced graft failure. Higher plasma lead concentration was associated with increased risk of graft failure (hazard ratio, 1.59 [95% CI, 1.14-2.21] per doubling; *P* = 0.006) independent of age, sex, transplant characteristics, estimated glomerular filtration rate, proteinuria, smoking status, alcohol intake, and plasma concentrations of cadmium and arsenic. These findings remained materially unchanged after additional adjustment for dietary intake and were consistent with those of analyses examining lead categorically. In serial measurements, plasma lead concentration was significantly higher at admission for transplant than at 3 months after transplant (*P* = 0.001), after which it remained stable over 2 years of follow-up (*P* = 0.2).

Limitations: Observational study design.

Conclusions: Pretransplant plasma lead concentrations, which decrease after transplant, are associated with increased risk of late kidney allograft failure. These findings warrant further studies to evaluate whether preventive or therapeutic interventions to decrease plasma lead concentration may represent novel risk-management strategies to decrease the rate of kidney allograft failure.

Chronic kidney disease (CKD) is a major global public health concern, and kidney transplant is the gold-standard kidney replacement therapy. Extensive research in recent decades has made it possible to significantly improve 1-year graft survival rates, but long-term graft survival continues to lag behind.[1] The need for improved kidney allograft survival is demonstrated by the fact that late graft failure is an increasingly important indication for dialysis or repeat transplant.[2] In the past few decades, the number of patients returning to dialysis after graft failure has increased,[3] and graft failure is one of the most frequent indications to start dialysis treatment in the United States.[4]

Graft failure is multifactorial and can be caused by immune and nonimmune mechanisms against a background of various donor and recipient risk factors.[5] There is great need to identify potentially modifiable, yet otherwise overlooked, risk factors. Heavy metal exposure may be such a risk factor because it is an established cause of kidney damage in native kidneys.[6] In recent studies, we have shown that plasma cadmium and arsenic levels are each associated with increased risk of graft failure in kidney transplant recipients (KTRs).[7,8] Another toxic heavy metal, lead, can be found in construction sites, paint, children's jewelry, folk remedies, glazed pottery, and even candy.[9] Although occupational exposure is especially relevant in developing countries,[10] in developed countries such as The Netherlands, significant amounts of lead can be found in topsoil from construction sites, disposal of coal ashes, and fertilization of land with city waste, which can cause lead to end up in food.[11] Cereals, milk, fruits, vegetables, and nonalcoholic beverages (including tea and fruit juices) have been shown to contribute the most to

PLAIN-LANGUAGE SUMMARY

Heavy metals are known to induce kidney damage, and transplanted kidneys may be particularly susceptible. Recent evidence showed that plasma concentrations of the heavy metals cadmium and arsenic are associated with increased risk of kidney graft failure. It is unknown if this association is also true for plasma lead concentrations. We measured plasma lead concentrations in 670 kidney transplant recipients with a functioning graft for ≥1 year who were followed for approximately 5 years at our outpatient clinic in Groningen, The Netherlands. Plasma lead concentrations were independently associated with an increased risk of late kidney graft failure, suggesting that lead-targeted interventions could be examined in future research as novel strategies to decrease the burden of kidney allograft failure.

total lead intake from food.[11] Cigarette smoking, alcoholic beverages, and urban drinking water have also been identified as important sources.[12-14] Interestingly, it has been suggested that, even though the calculated intake of lead in the Dutch population is below the European Food Safety Authority's proposed limits of exposure for augmented risk of developing systemic diseases, detrimental health effects cannot be excluded.[11,15] In fact, the Dutch Health Council recently identified lead-containing water service pipes as a relevant source of overexposure to lead and recommended avoidance in vulnerable groups such as pregnant women, infants, and young children.[16]

In adults, the kidneys are among the organs most affected by lead burden.[17] Chronic exposure results in glomerular dysfunction and chronic tubulointerstitial nephritis, ultimately leading to fibrosis.[18] Oxidative stress has been suggested to be the main mechanism underlying lead-associated toxicity.[19] Lead inactivates functional thiol groups in antioxidant enzymes and molecules,[20] which can also enhance the toxicity of other metals,[19] leading to lipid peroxidation and loss of membrane integrity in kidney cells.[21]

Minor exposures to lead can have nephrotoxic effects, especially in patients with hypertension, diabetes, or existing CKD.[22,23] KTRs are especially susceptible to oxidative agents as a result of chronic exposure to oxidative challenges, including a large burden of the aforementioned concomitant conditions, but also because of maintenance immunosuppressive therapy and decreased kidney function. We hypothesize that lead exposure represents an as-yet overlooked risk for decreased long-term graft function, thereby representing a potentially modifiable risk factor to which clinical monitoring and therapeutic interventions may be applicable.

In the present study, we determined plasma lead concentrations in a large cohort of KTRs from the TransplantLines Food and Nutrition Biobank and Cohort Study and investigated the association with late kidney graft failure. We additionally studied changes in plasma lead concentration before and after transplant in patients from the ongoing TransplantLines Biobank and Cohort Study.[24]

Methods

Study Population

Between November 2008 and March 2011, all adult KTRs with a functioning allograft for ≥1 year who visited the outpatient clinic of the University Medical Center Groningen (Groningen, The Netherlands) were invited to participate in the TransplantLines Food and Nutrition Biobank and Cohort Study (ClinicalTrials.gov identifier NCT02811835) as described previously.[7] A total of 707 of 817 (87%) eligible KTRs signed informed consent. Pancreas transplant patients (n = 1) and patients without plasma lead measurements (n = 36) were excluded from the present analyses, resulting in 670 KTRs (Fig S1) at a median of 5.4 (interquartile range [IQR], 1.9-11.8) years after transplant. The study protocol was approved by the institutional review board (METc 2008/186) and was conducted in accordance with the Declaration of Helsinki.

To investigate intraindividual variability of plasma lead levels before transplant and over time after transplant, we requested follow-up plasma samples (at admission for kidney transplant and at 3, 6, 12, and 24 months after transplant) from 46 KTRs consecutively enrolled between February 2016 and May 2017 in the ongoing TransplantLines Prospective Cohort and Biobank Study (ClinicalTrials.gov identifier NCT03272841; Fig S2).[24] To additionally investigate whole-blood lead compared with plasma lead concentrations, we also collected plasma and whole-blood samples of 122 KTRs (Fig S3) at a median of 4.9 (IQR, 1.4-10.9) years after transplant (ie, with a transplant vintage comparable to baseline measurement of plasma lead in the 670 KTRs in the main patient cohort of the present study).

Data Collection and Definitions

All patients received transplants at University Medical Center Groningen and were treated with standard immunosuppressive therapy (described in Item S1) as detailed elsewhere.[25] Medical and transplant history as well as medication use were extracted from electronic patient records. Patients were asked to collect a 24-hour urine specimen during the day before their outpatient clinic. Blood was drawn the morning after completion of the 24-hour urine collection. The measurement of clinical and laboratory parameters has been previously described.[7] To investigate whether dietary exposure is associated with plasma lead levels,[11] dietary intake was assessed using a validated semiquantitative food frequency questionnaire developed and updated at Wageningen University.[26] To fill

out the questionnaire, participants were asked about their intake of 177 food items during the previous month, taking seasonal variations into account. For each item, the frequency was expressed in times per day, week, or month. The number of servings was recorded in natural units (eg, slice of bread or apple) or household measures (eg, cup or spoon). The food frequency questionnaire was self-administered and then checked by a trained researcher on the day of the visit to the outpatient clinic. Inconsistent answers were verified with the patients. The results of the questionnaire were converted into total energy and nutrient intake per day using the Dutch Food Composition Table of 2006. Information on alcohol consumption and smoking behavior was obtained by questionnaires.[26] History of diabetes was defined as the use of antidiabetic medication or a fasting blood glucose level ≥7.0 mmol/L. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation.[27]

Lead, Cadmium, and Arsenic Analyses

Whole-blood and plasma lead concentrations were determined with an inductively coupled plasma mass spectrometer (820-MS; Varian) with a validated method for the measurement of heavy metals as previously reported.[7,8] Standards were made by addition to blank blood or plasma of known amounts of lead to obtain added concentrations of 2.5, 5, 10, 15, 20, and 25 μg/L. Control samples were made by spiking blank blood or plasma with known amounts of lead to obtain added concentrations of 7.5, 25.0, and 45.0 μg/L (low, medium, and high, respectively). Sample preparation consisted of diluting a 100-μL sample with 1.0 mL dilution reagent (which contained 0.005% Triton X-100, 0.005% EDTA, and 0.1 mg/L yttrium as an internal standard). Characteristics of this method are summarized in Table S1. Plasma cadmium and arsenic were determined as detailed previously.[7,8]

Clinical End Points

The primary end point of this study was graft failure, defined as the requirement of dialysis or repeat transplant, in adherence with current recommendations and state of the art in the field.[28] Death with a functioning graft (n = 112) was a competing event. The surveillance system of the outpatient program at our university hospital ensures updated information on patient status and events of graft failure as assessed by a nephrologist. Within this system, patients visit the outpatient clinic with decreasing frequency in accordance with the guidelines of the American Society of Transplantation. End points were recorded until September 2015. General practitioners or referring nephrologists were contacted in case the status of a patient was unknown. No patients were lost to follow-up.

Statistical Analyses

Data analyses were performed using SPSS 27.0 for Windows (IBM) and R version 3.2.3 (R Foundation for Statistical Computing). Baseline characteristics of study participants were described by subgroups of patients according to tertiles of plasma lead distribution. Normally distributed variables are described as mean ± standard deviation and skewed variables as median (IQR). Categorical variables are expressed as number with percentage. Differences were studied using the χ^2 test or Fisher exact test for categorical variables and linear regression analyses for continuous variables. Residuals of linear regression were checked. Variables were $\log_2$-transformed when appropriate. A 2-sided P value <0.05 was considered significant.

Box plots were used to illustrate median (IQR) plasma lead levels at admission for transplant and at posttransplant follow-up visits. Significance of potential difference between plasma lead at admission for transplant and 3 months after transplant was tested using the Wilcoxon matched-pairs signed rank test, and significance of potential change during post–kidney transplant follow-up visits was tested using one-way repeated-measure analysis of variance. To investigate posttransplant intraindividual variability of $\log_2$-transformed plasma lead concentrations, we calculated the intraindividual coefficient of variation for posttransplant follow-up plasma lead levels as (standard deviation/mean) × 100, in which "mean" is the mean value of $\log_2$-transformed plasma lead concentrations. The associations between plasma lead and plasma cadmium and plasma arsenic were studied by means of linear regression analyses. Residuals were checked for normality and $\log_2$-transformed when appropriate.

Prospective Analyses

In prospective analyses of the primary end point of graft failure, the association of baseline lead concentration (assessed from samples taken at a median of 5.4 [IQR, 1.9-11.8] years after transplant, which was the start of the current prospective study) with risk of graft failure was examined incorporating time to event by means of cause-specific hazards models. For these analyses, the competing risk of death with a functioning graft was accounted by censoring at time of death. Schoenfeld residuals were calculated to assess whether proportionality assumptions were satisfied. The association of lead with risk of graft failure was analyzed as a continuous and a categorical variable. In cause-specific hazards models with continuous variables, plasma lead was $\log_2$-transformed to estimate regression coefficients per doubling of plasma lead concentration. For categorical analyses, participants were divided according to tertiles of plasma lead concentration. To account for potential confounders, several multivariable-adjusted cause-specific hazards models were fitted to the data. We adjusted for demographic characteristics, kidney transplant characteristics, and lifestyle-related exposure to lead (age, sex, transplant vintage, warm ischemia time, donor type, eGFR,

proteinuria, smoking status, and alcohol intake) in model 1. Further models were performed with additional adjustments to model 1 (primary model). Thus, subsequently, we additively adjusted for cooccurring prooxidant conditions (ie, history of hypertension and diabetes) in model 2; history of cardiovascular disease and dyslipidemia (ie, triglycerides and high-density lipoprotein cholesterol, and use of statins) in model 3; cereal, vegetable, fish, and seafood intake in model 4; and plasma cadmium and plasma arsenic (model 5). Covariates were handled as linear variables unless they were primarily collected as categorical variables (ie, history of hypertension, diabetes, use of statins). To illustrate the association of plasma lead with risk of graft failure, data were fitted using median plasma lead concentration (0.31 µg/L) as reference value (HR of 1.00) to estimate and plot regression coefficients.

Potential effect modification by age, sex, systolic blood pressure, eGFR, calcium, parathyroid hormone, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, triglycerides, diabetes, and cadmium levels were tested by fitting models containing main effects and their cross-product terms. The Bonferroni-adjusted significance threshold ($P < 0.004$ for interaction) was considered to indicate the presence of significant effect modification, after which further evaluation proceeded through stratified prospective analyses.

Results

Baseline Characteristics

We included 670 KTRs (mean age, 53 ± 13 years; 58% male) at a median of 5.4 (IQR, 1.9-11.8) years after transplant. Mean eGFR was 52 ± 20 mL/min/1.73 m². Median lead concentration was 0.31 (IQR, 0.22-0.45) µg/L. Details of baseline characteristics by tertile of plasma lead concentration are shown in Table 1. With a higher plasma lead concentration tertile, participants were significantly more likely to be of older age, male, and former smokers and have higher intake of potatoes and higher plasma concentrations of calcium, parathyroid hormone, alkaline phosphatase, triglycerides, and cadmium. Transplant vintage and incidence of living-donor kidney transplant were significantly lower with higher plasma lead concentration tertile.

Linear regression analyses of log₂-transformed plasma lead concentration versus other potentially cooccurring heavy metal exposures, ie, log₂-transformed plasma cadmium and arsenic concentrations, are shown in Fig 1. We found that higher plasma cadmium concentration is associated with higher plasma lead levels, whereas this was not so for plasma arsenic levels. This may be due to overlapping or usually cooccurring sources of exposure to cadmium and lead (smoking and alcohol intake, respectively).[14]

Prospective Analyses of the Association Between Lead and Risk of Graft Failure

During a median follow-up of 4.9 (IQR, 3.4-5.5) years after baseline lead concentration determination, 78 KTRs experienced graft failure (12%; event rate, 78 per 3,270 patient-years). Higher plasma lead concentrations were associated with increased risk of graft failure (HR, 1.59 [95% CI, 1.14-2.21] per doubling of plasma lead concentration; $P = 0.006$) independent of adjustment for age, sex, transplant vintage, donor type, warm ischemia time, smoking status, alcohol intake, eGFR, and proteinuria (Fig 2; Table 2). Similarly, in categorical analyses according to tertiles of plasma lead distribution, higher plasma lead level was significantly associated with increased risk of graft failure ($P = 0.01$ for trend). These findings remained materially unchanged in further multivariable-adjusted analyses.

Analyses for Potential Effect Modification

Results of analyses for assessment of potential effect modification of the association between plasma lead and risk of graft failure are shown in Table S2. We did not find evidence of effect modification.

Serial Plasma Lead Levels in KTRs in the TransplantLines Cohort and Biobank Study

Plasma lead concentrations at admission for transplant and at different follow-up visits after transplant were investigated in 46 KTRs (mean age, 52 ± 14 years; eGFR, 43 ± 28 mL/min/1.73 m²) from the ongoing TransplantLines Prospective Cohort and Biobank Study. Figure 3A shows that plasma lead concentration at admission for transplant was significantly different from plasma lead concentration at 3 months after transplant (medians of 2.34 [IQR, 1.81-2.95] and 2.11 [IQR, 1.52-2.62] µg/L, respectively; $P = 0.001$). Figure 3B shows that plasma lead concentration at transplant was significantly associated (standardized β = 0.61, $P < 0.001$) with plasma lead concentration at 3 months after transplant ($R^2 = 0.37$). Figure 4 shows box plots with median plasma lead concentrations at different follow-up visits after transplant (2.11 [IQR, 1.53-2.62], 2.01 [IQR, 1.55-2.28], 2.19 [IQR, 1.48-2.52], and 2.09 [IQR, 1.64-2.39] ng/L at 3, 6, 12, and 24 months after transplant, respectively). Median intraindividual coefficient of variation after transplant was 15% (IQR, 6%-32%), and we did not find signs of a significant change in plasma lead levels after transplant ($P = 0.2$, one-way repeated-measures analysis of variance). The distribution of the intraindividual coefficient of variation is shown in Fig S4.

Blood Versus Plasma Lead Levels in KTRs in the TransplantLines Cohort and Biobank Study

Figure S5 shows the association of whole-blood lead (mean, 29.82; median, 21.50 [IQR, 15.18-37.18]; range, 7.10-114.0 µg/L) with plasma lead (mean, 0.60; median, 0.40 [IQR, 0.30-0.70]; range, 0.20-3.10 µg/L)

Table 1. Baseline Characteristics of 670 Kidney Transplant Recipients

| Characteristic | Plasma Lead Concentration | | | |
	Tertile 1: ≤0.24 µg/L (n = 224)	Tertile 2: 0.24-0.38 µg/L (n = 224)	Tertile 3: ≥0.38 µg/L (n = 222)	P for trend
Lead, µg/L	0.19 [0.16-0.22]	0.31 [0.27-0.35]	0.53 [0.45-0.72]	–
Demographic/anthropometric				
Age, y	50 ± 13	53 ± 13	56 ± 12	<0.001
Male sex	107 (48%)	145 (65%)	133 (60%)	0.001
Body mass index, kg/m²	26.3 ± 5.1	26.8 ± 4.2	26.9 ± 4.9	0.4
Diabetes	57 (25%)	52 (23%)	54 (24%)	0.9
Smoking status				0.01
Never	107 (48%)	87 (39%)	72 (32%)	
Former	81 (36%)	96 (43%)	107 (48%)	
Current	25 (11%)	27 (12%)	28 (13%)	
Alcohol use				0.9
0 g/d	23 (10%)	22 (10%)	30 (14%)	
>0-10 g/d	134 (60%)	121 (54%)	113 (51%)	
10-30 g/d	37 (17%)	53 (24%)	40 (18%)	
>30 g/d	5 (2%)	12 (5%)	13 (6%)	
History of CVD	93 (42%)	102 (46%)	100 (45%)	0.7
Systolic BP, mm Hg	134 ± 17	136 ± 17	138 ± 18	0.2
Diastolic BP, mm Hg	82 ± 11	83 ± 11	83 ± 11	0.6
Use of antihypertensive medication	192 (86%)	193 (86%)	205 (92%)	0.06
Kidney function and transplant history				
eGFR, mL/min/1.73 m²	55 ± 21	51 ± 20	52 ± 19	0.2
Proteinuria	47 (21%)	54 (24%)	49 (22%)	0.7
Transplant vintage, y	6 [2-14]	7 [3-12]	4 [1-9]	<0.001
Acute rejection	65 (29%)	65 (29%)	46 (21%)	0.07
Cold ischemia time, h	13 [3-21]	15 [3-21]	15 [3-21]	0.2
Warm ischemia time, min	43 ± 15	42 ± 14	45 ± 17	0.04
HLA mismatches	2.2 ± 1.6	2.1 ± 1.5	2.4 ± 1.6	0.7
Living donor	93 (42%)	80 (36%)	58 (26%)	0.003
Primary kidney disease				0.5
Glomerulosclerosis	66 (30%)	72 (32%)	52 (23%)	
Glomerulonephritis	21 (9%)	15 (7%)	15 (7%)	
Tubulointerstitial nephritis	25 (11%)	28 (13%)	22 (1%)	
Polycystic kidney disease	42 (19%)	45 (20%)	54 (24%)	
Kidney hypoplasia or dysplasia	14 (6%)	8 (4%)	7 (3%)	
Renovascular disease	10 (5%)	12 (5%)	17 (8%)	
Diabetes	9 (4%)	11 (5%)	12 (5%)	
Other/miscellaneous	37 (17%)	33 (15%)	43 (19%)	
Records of immunosuppressive therapy				
Use of calcineurin inhibitor	124 (55%)	127 (57%)	133 (60%)	0.6
Use of proliferation inhibitor	185 (83%)	187 (84%)	186 (84%)	0.9
Corticosteroid dose <10 mg/d	101 (45%)	92 (41%)	81 (37%)	0.2
Dietary intake				
Cereals, g/d	182 [138-227]	176 [125-225]	172 [134-218]	0.9
Potatoes, g/d	100 [60-150]	119 [60-158]	119 [60-160]	0.04
Vegetables, g/d	81 [55-121]	79 [56-119]	75 [48-115]	0.7
Fruits, g/d	104 [47-189]	107 [51-199]	107 [48-178]	0.5
Nuts, g/d	4.8 [0.0-9.6]	3.0 [0.7-9.4]	3.5 [0.0-8.9]	0.3
Fish and seafood, g/d	10.5 [4.0-18.7]	11.7 [4.7-23.0]	11.5 [3.9-20.0]	0.2
Meat, g/d	94 [69-114]	91 [71-118]	97 [73-119]	0.2
Milk and dairy products, g/d	377 [251-498]	347 [229-488]	369 [235-536]	0.5
Laboratory measurements				
Calcium, mmol/L	2.38 ± 0.14	2.39 ± 0.15	2.43 ± 0.15	<0.001
Parathyroid hormone, pmol/L	8.4 [5.9-13.8]	9.8 [6.4-15.0]	10.2 [6.8-17.0]	0.03

(Continued)

Table 1 (Cont'd). Baseline Characteristics of 670 Kidney Transplant Recipients

Characteristic	Plasma Lead Concentration			
	Tertile 1: ≤0.24 µg/L (n = 224)	Tertile 2: 0.24-0.38 µg/L (n = 224)	Tertile 3: ≥0.38 µg/L (n = 222)	*P* for trend
FGF-23, RU/mL	58 [42-98]	66 [44-98]	62 [43-99]	0.5
Total cholesterol, mmol/L	5.0 ± 1.1	5.2 ± 1.1	5.1 ± 1.1	0.09
HDL cholesterol, mmol/L	1.3 ± 0.4	1.4 ± 0.5	1.4 ± 0.5	0.9
LDL cholesterol, mmol/L	2.8 [2.2-3.6]	2.9 [2.4-3.5]	2.9 [2.3-3.5]	0.1
Triglycerides, mmol/L	1.7 [1.2-2.2]	1.7 [1.2-2.3]	1.8 [1.3-2.5]	0.01
Glucose, mmol/L	5.3 [4.7-6.1]	5.2 [4.7-6.0]	5.3 [4.9-6.2]	0.5
HbA$_{1c}$, %	6.0 ± 0.9	5.9 ± 0.7	6.1 ± 0.9	0.8
Cadmium, µg/L	0.05 [0.04-0.06]	0.06 [0.04-0.07]	0.07 [0.05-0.09]	<0.001
Arsenic, µg/L	1.23 [1.04-1.86]	1.31 [1.05-2.23]	1.24 [1.02-2.01]	0.3

Values for continuous variables presented as mean ± standard deviation or median [interquartile range]. Differences among tertiles of the plasma lead distribution were studied by means of analysis of variance or the linear regression test for continuous variables and by means of the χ^2 test for categorical variables. Abbreviations: eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HLA, human leukocyte antigen; LDL, low-density lipoprotein; CVD, cardiovascular disease; RU, relative unit; BP, blood pressure; HbA$_{1c}$, hemoglobin A$_{1c}$.

concentration (standardized β = 0.68; P < 0.001) in 122 KTRs in the TransplantLines Prospective Cohort and Biobank Study.

Discussion

This study of a large cohort of KTRs shows that plasma lead concentration is associated with increased risk of late kidney graft failure. Our results were independent of adjustment for age, sex, transplant characteristics, eGFR, proteinuria, smoking status, history of hypertension and diabetes mellitus; dietary intake of cereals, vegetables, fish, and seafood; and plasma concentrations of cadmium and arsenic. These results suggest that lead exposure may be a potentially modifiable, yet previously overlooked, risk factor for late graft failure in KTRs, underscoring the question whether plasma lead monitoring and therapeutic interventions to decrease its levels might diminish the burden of late graft failure in KTRs.
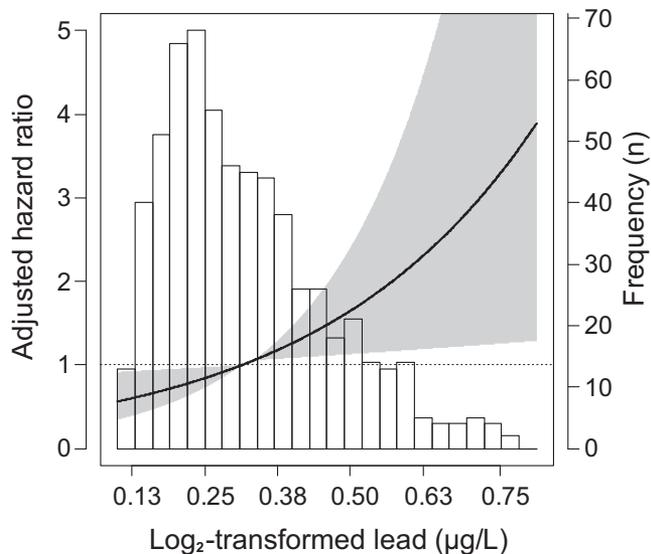
We found lower plasma and whole-blood lead concentrations than previous studies in the general population (eg, mean lead concentrations of 0.54 and 119 µg/L, respectively[29]) and occupational cohorts (eg, geometric mean lead concentrations of 0.57 and 227 µg/L, respectively[30]). In a large (N = 15,211) representative sample of the civilian noninstitutionalized US population participating in the Third National Health and Nutrition Examination Survey, mean blood lead concentrations were 42.1 and 33.0 µg/L, respectively, in participants with and without hypertension,[23] which are also higher than the blood lead levels than in our study. Evaluating the relationship between plasma and blood lead concentrations, Smith et al[31] described a curvilinear relationship, with the mean ratio of plasma to whole-blood lead in the 0.308%-0.291% range. The median baseline plasma lead concentration in the present cohort of 670 KTRs was 0.31 µg/L. Using the ratio of 0.3% reported by Smith et al, this value would correspond to a whole-blood lead concentration of 103 µg/L, which is approximately 5 times higher than the whole-blood lead concentration we found. This suggests a much higher plasma lead–to–whole-blood lead ratio in the KTRs in our study than in the general population.

Of potential relevance, lead is known as a "bone-seeking" element, with lead from blood first being incorporated in bone and released from it later at rates depending on bone turnover rates.[32] Because plasma lead–to–whole-blood lead ratios have consistently found to be more strongly associated with bone lead levels than whole-blood lead concentrations,[31] this could indicate that plasma lead concentrations are more closely related to bone lead levels than whole-blood lead concentrations. Given that secondary and tertiary hyperparathyroidism
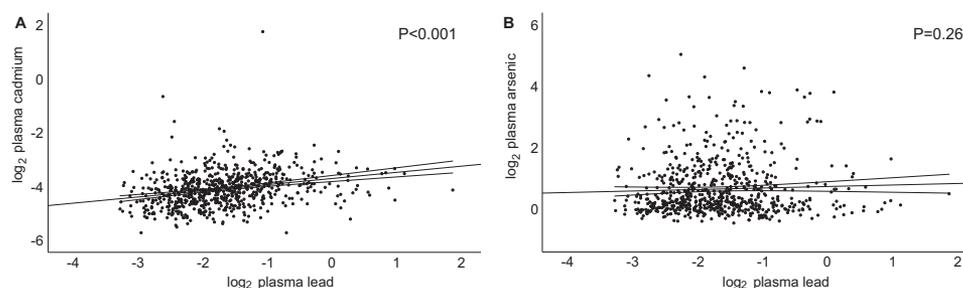
Figure 1. Linear regression analyses of the association between plasma levels of lead and (A) cadmium (standardized β = 0.27, *P* < 0.001) and (B) arsenic (standardized β = 0.04, *P* = 0.3).

Figure 2. Association of plasma lead concentration with risk of graft failure in kidney transplant recipients. Data were fitted by cause-specific hazards models using median lead concentration (0.31 µg/L) as reference value. The black line represents the hazard ratio, and the gray area represents the 95% CI.

is a special entity, with most rapid net bone loss in the first year after transplant, followed by more mitigated, but continued, loss thereafter.[33] The high rate bone loss in the early phase after transplant may set more lead free from bone, and this itself, or circumstances accompanying it (eg, low phosphate concentrations or acidosis),[34] may shift the equilibrium between plasma lead and whole-blood lead toward relatively high concentrations of the former. It would be of interest if future studies could investigate the association of plasma lead and whole-blood lead with metabolic milieu and bone turnover early and late after transplant.

Previous literature has linked lead exposure to decreased kidney function,[22,35] contributing to deterioration of kidney function in the general population[36] and in patients with CKD.[23,37] Our findings are in agreement with the evidence pointing toward the kidney as a relevant site of lead toxicity,[38] with chronic exposure inducing progressive proximal tubular atrophy, interstitial fibrosis, and vascular changes.[18,22,39] Because higher blood lead levels are associated with increased risk of hypertension,[40] it could be hypothesized that at least part of the lead-associated risk of graft failure is attributable to an intermediary role of increased blood pressure in KTRs.[4] Although it was not statistically significant, we observed nominally higher systolic blood pressures at greater tertiles of plasma lead concentration and a borderline higher use of antihypertension medication in patients with higher plasma lead levels. However, the association between lead concentration and graft failure was independent of hypertension, which may suggest that plasma lead level is associated with risk of late graft failure mainly by direct mechanisms of nephrotoxicity.

Food, tobacco, and alcohol consumption are the most relevant sources of lead exposure in the general population.[12-14] In The Netherlands, particularly, water service pipes have been identified as a relevant source of over-exposure to lead.[16] Lead is available in organic and inorganic forms. Inorganic lead is not metabolized, but distributed, and deposited in soft tissues and bones.[17] Because we found plasma lead concentrations to be positively associated with plasma calcium concentration,

leading to high bone turnover are very common in KTRs[33] but very uncommon in the general population, it is conceivable this could play a role in a higher plasma lead–to–whole-blood lead ratio in KTRs than in the general population. Interestingly, we also found that the group of KTRs with serial plasma lead measurements (n = 46) had approximately 10-fold higher plasma lead concentrations than the 670 KTRs in the main patient cohort in the present study. Of note, the KTRs with the 10-fold higher plasma lead concentrations were studied at a rather short transplant vintage (3-24 months after transplant) compared with the 670 patients in the main cohort (median, 5.4 [IQR, 1.9-11.8] years after transplant). It is possible that the high plasma lead concentrations in the early phase after transplant are reflective of the bone-seeking tendencies of lead[32] considering that it is widely acknowledged that post–kidney transplant osteodystrophy

Table 2. Association of Lead With Risk of Graft Failure

	Lead, per log$_2$ greater, µg/L		HR (95% CI)		
	HR (95% CI)	P	Lead Tertile 1	Lead Tertile 2	Lead Tertile 3
Model 1	1.59 (1.14-2.21)	<0.006	1.00 (reference)	0.95 (0.46-1.96)	2.11 (1.03-4.33)
Model 2	1.60 (1.15-2.24)	0.006	1.00 (reference)	0.91 (0.43-1.90)	2.12 (1.03-4.35)
Model 3	1.60 (1.14-2.26)	0.007	1.00 (reference)	1.03 (0.48-2.20)	2.18 (1.03-4.57)
Model 4	1.54 (1.10-2.16)	<0.01	1.00 (reference)	0.94 (0.45-1.95)	1.94 (0.93-4.03)
Model 5	1.56 (1.11-2.18)	<0.01	1.00 (reference)	0.94 (0.45-1.93)	1.94 (0.94-4.02)

Cause-specific hazards models were performed to assess the association of plasma lead concentration with death-censored graft failure (events, n = 78). Associations are shown with plasma lead concentration as a continuous variable and according to tertiles of the plasma lead distribution (tertile 1, ≤0.24 µg/L; tertile 2, 0.25-0.38 µg/L; tertile 3, ≥38 µg/L). Models were adjusted for age, sex, transplant vintage, donor type, warm ischemia time, smoking status, alcohol intake, estimated glomerular filtration rate, and proteinuria (model 1). Further models were performed with additional adjustments to model 1 (primary model) as follows: history of hypertension and diabetes mellitus (model 2); history of cardiovascular disease and triglycerides, high-density lipoprotein cholesterol, and use of statins (model 3); cereals, vegetables, fish, and seafood intake (model 4); and plasma cadmium and plasma arsenic (model 5).
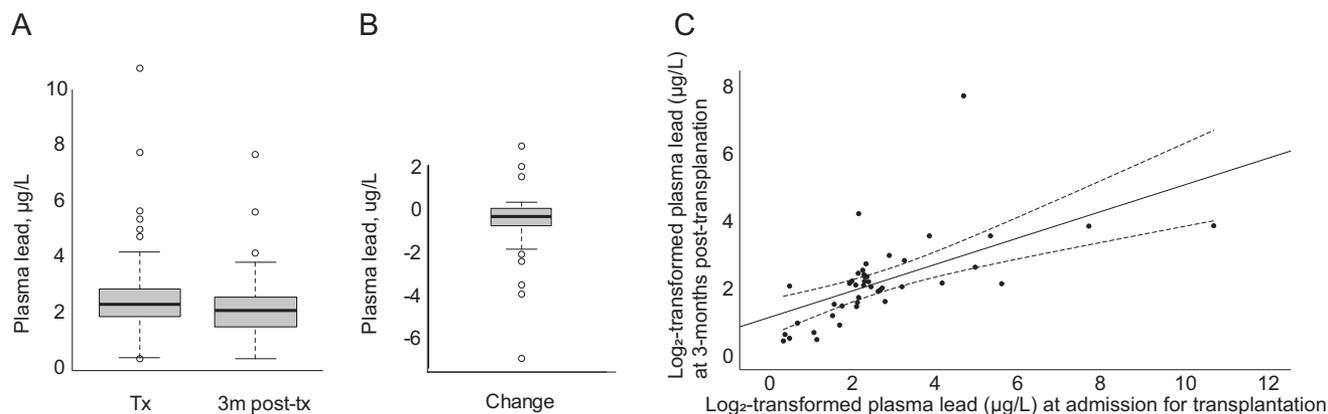
Figure 3. Plasma lead concentrations at admission before transplant (Tx) and at 3 months (3m) after transplant in 46 kidney transplant recipients in the TransplantLines Prospective Cohort and Biobank Study. (A-B) Plasma lead concentration at 3 months after transplant was significantly different from plasma lead concentration at admission for transplant (medians of 2.11 [interquartile range (IQR), 1.52-2.62] and 2.34 [IQR, 1.81-2.95] μg/L, respectively; $P = 0.001$). Box plots show median (IQR). Significance of the potential difference between lead concentrations at transplant and 3 months after transplant was tested using the Wilcoxon matched-pairs signed rank test. (C) Plasma lead concentration at transplant was significantly associated (standardized β = 0.61, $P < 0.001$) with plasma lead concentration at 3 months after transplant ($R^2 = 0.37$).

plasma concentrations of parathyroid hormone and alkaline phosphatase may be appreciated as a sign of the affinity of lead to bone and its acknowledged adverse effect on bone mineralization. After absorption, lead enters the bloodstream, where it is predominantly bound to erythrocyte proteins[41] with a half-life of approximately 35 days.[42] Clearance from circulation occurs through distribution into soft tissues and bone as well as excretion. A small amount of lead is excreted in feces, sweat, hair, and nails, and the main excretion is through kidney filtration and elimination in urine.[41] In human kidney cells, lead-
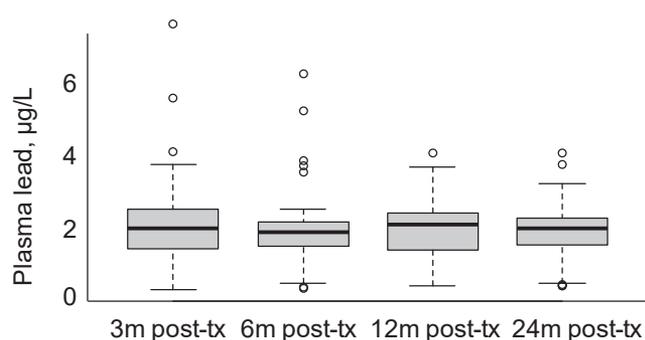
Figure 4. Plasma lead concentrations in 46 kidney transplant recipients in the TransplantLines Prospective Cohort and Biobank Study at different follow-up visits after transplant. Box plots show median (interquartile range). Significance of potential change during follow-up visits was tested using one-way repeated-measures analysis of variance, which indicated no significant change over time ($P = 0.2$). Median intraindividual coefficient of variation of plasma lead concentration was 15% (interquartile range, 6%-32%). The distribution of the intraindividual coefficient of variation is shown in Fig S3.

binding proteins have been identified, which are presumably endocytosed, entering proximal tubular epithelial cells.[43] At toxic levels, when inside the cells, these proteins tend to form inclusion bodies in the cytoplasm, which has a temporal correlation with the onset of tubular dysfunction.[44] It has been suggested that these inclusion bodies reduce cytoplasmic lead concentrations, allowing renal tubular epithelium to remain viable, albeit at a reduced functional level.[45] Plasma lead levels reflect exposure from exogenous sources plus the release of endogenous lead from bone. Plasma rather than blood levels reflect the fraction of circulatory lead that is more freely available for exchange with tissues[46] and that, in the kidney, is filtered to form the ultrafiltrate to which the kidney tubular epithelial cells are exposed, thus more closely signaling lead kidney burden for estimation of kidney function risk.[31]

Our findings are relevant for informing clinical follow-up of outpatient KTRs. Our findings may underscore the need to ask KTRs about occupation and hobbies with chemical exposures. In addition, chelation therapy, used in heavy-metal poisoning, may warrant further study as a potential interventional approach to reduce the burden of long-term graft failure in KTRs. Of note, it has been repeatedly shown that the urinary excretion of lead can be increased by using calcium-EDTA chelation, which in turn has proven to lessen progression rates of diabetic[47] and nondiabetic[48] nephropathy in patients with high-normal body lead burden, as well as progression of CKD in patients with increased body lead burden.[37]

It is worth noting that our study was conducted in a population from the northeastern region of The Netherlands, an area with known low lead environmental exposure compared with developing countries[49] or

industrial countries such as China, where child lead intoxication has been a much more severe health concern. Our data underscore that mildly increased plasma lead concentrations (higher than approximately 0.30 μg/L, but much lower than 5 μg/L as previously indicated by Ekong et al[22]) may be a risk factor associated with impaired long-term graft function in KTRs. We acknowledge that our study population was predominantly White and derived from a single center from the northern part of The Netherlands and may not be generalizable to other populations with different environmental contamination and exposure to lead.

Point estimates of hazard ratios in the prospective analyses remained materially unchanged after adjustment for intake of particular foods, suggesting that food sources may not be a major route of exposure. We also acknowledge potential confounding effects of low socioeconomic status, which is linked, at least in the United States, to high lead exposure as a result of lead-based paint and lead pipes, faucets, and plumbing fixtures.[50] Further studies are needed to better determine exposure routes and the association between exposure and circulating lead levels. In our study of serial plasma lead levels in a sample population of the TransplantLines Cohort and Biobank Study,[24] we found low intraindividual variability, indicative of relatively stable plasma lead levels over time after transplant. It should be noted that we used posttransplant plasma lead concentrations as the baseline lead concentration for the prospective analyses of the association with graft failure, which assumes that the plasma lead concentrations did not change over time in the patients included in these analyses. Although we found no evidence for changes over time in plasma lead concentration after transplant, this remains a rather strong assumption, which requires confirmation in further studies. Although several investigators have suggested that plasma lead represents a more relevant index of exposure to health risks associated with lead than does whole-blood lead, because plasma lead may better reflect the fraction of circulatory lead that is more freely available for exchange with tissues,[31,32] it is also true that research on associations between plasma lead and toxicologic outcomes is still sparse, and a significant gap in knowledge remains.[32] It has been suggested that plasma lead measurement is too imprecise to be useful in individuals with low-level exposure, and whole-blood lead concentration may be a useful biomarker in this situation.[30] However, we found a strong association between plasma lead level and long-term outcome, which suggests that plasma lead concentrations are a meaningful biomarker, at least in KTRs. Further studies are needed to determine whether plasma lead levels detected with the newest and most sensitive inductively coupled plasma mass spectrometry equipment serve as a meaningful biomarker in other populations and whether it can be used as an alternative to whole-blood lead concentrations or even outperform it as a biomarker. Finally, as a result of its observational nature, the present study does not prove causality. Residual confounding may occur despite adjustment for potential confounders.

Our results show that plasma lead level is independently associated with risk of late kidney graft failure, indicating the need for future studies to confirm our results and externally validate our findings among different populations of KTRs. Lead exposure may be a potentially modifiable risk factor for adverse long-term kidney graft outcomes. Whether clinical monitoring of lead concentrations, reduction of environmental exposure, and nontoxic therapeutic interventions (eg, chelation) to decrease system lead concentrations in KTRs may represent novel risk-management strategies to decrease the burden of long-term kidney graft failure remains to be investigated.

Supplementary Material

Supplementary File (PDF)

Figure S1: Flowchart for main study population.

Figure S2: Flowchart for patients with longitudinal follow-up from the ongoing TransplantLines Prospective Cohort and Biobank Study.

Figure S3: Flowchart for patients from the ongoing TransplantLines Prospective Cohort and Biobank Study with a transplant vintage at baseline comparable to that of the main study population.

Figure S4: Distribution of the intraindividual coefficient of variation of plasma lead at 3, 6, 12, and 24 months after transplant in 46 KTRs in the ongoing TransplantLines Prospective Cohort and Biobank Study.

Figure S5: Association of whole-blood lead with plasma lead in 122 KTRs in the TransplantLines Prospective Cohort and Biobank Study.

Item S1: Immunosuppressive therapy.

Table S1: Bias and precision of lead measurements in whole blood and in plasma using standard addition of known amounts of lead

Table S2: Potential effect modifiers of the association between lead level and risk of graft failure

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Plasma Lead and Risk of Late Kidney Allograft Failure: Findings From the TransplantLines Biobank and Cohort Studies

Design and Methods

670 kidney transplant recipients

With a functioning graft ≥1 year

Baseline phenotyping including plasma lead (Pb) measurement

Median follow-up ~5 years

Results

Median Pb 0.31 µg/L (IQR, 0.22–0.45)

78 graft failure events

HR 1.59 95% CI 1.14–2.21 per doubling of plasma Pb

Major Finding

Risk of Graft Failure
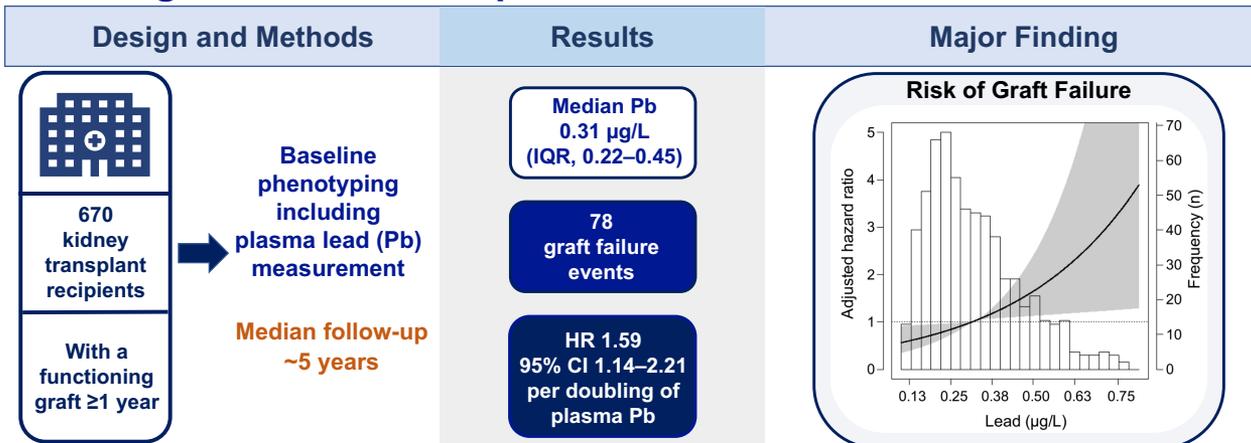
CONCLUSION: Plasma lead is independently associated with increased risk of late kidney graft failure.

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