Lead-related nephrotoxicity: A review of the epidemiologic evidence

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Chronic kidney disease (CKD) represents a major global public health concern. Efforts to prevent and/or slow progression of CKD are essential. Lead nephropathy, characterized by chronic tubulointerstitial nephritis, is a well-known risk of chronic, high-level lead exposure. However, in recent years, lead exposure has declined sharply, particularly in developed countries. We reviewed epidemiologic research in general, occupational, and patient populations to assess whether lead, at current exposure levels, still contributes to nephrotoxicity. Other pertinent topics, such as risk in children, genetic susceptibility, and coexposure to cadmium, are also considered. The data reviewed indicate that lead contributes to nephrotoxicity, even at blood lead levels below 5 μg/dl. This is particularly true in susceptible populations, such as those with hypertension (HTN), diabetes, and/or CKD. Low socioeconomic status is a risk factor for both lead exposure and diseases that increase susceptibility. Future public health risk for lead-related nephrotoxicity may be most significant in those rapidly developing countries where risk factors for CKD, including obesity and secondary HTN and diabetes mellitus, are increasing more rapidly than lead exposure is declining. Global efforts to reduce lead exposure remain important. Research is also needed to determine whether specific therapies, such as chelation, are beneficial in susceptible populations.

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Chronic kidney disease (CKD) represents a major public health concern. A recent analysis of US National Health and Nutrition Examination Survey data estimated that 19 million Americans have CKD, which includes end-stage renal disease and the four stages of renal dysfunction that precede it.[1] Worldwide, the estimated number of end-stage renal disease patients increased from 886 023 in 1999 to 1 131 594 in 2003.[2] Prevalence rates vary and are much higher in certain groups. In the US, for example, African-Americans have rates of end-stage renal disease that are four times higher than those in Caucasians.[2] Despite improvements in therapy, mortality remains substantial. Fewer than 40% of patients survive more than 5 years after onset of dialysis.[2] Recent data indicate that obesity is also increasing globally,[3,4] resulting in greater prevalence of diabetes mellitus and hypertension (HTN),[5–8] which are the leading causes of CKD. Obesity may increase CKD risk by other pathways as well.[9]

In this setting, strategies to prevent CKD and/or slow progression at earlier stages are imperative and will require a global effort. Exposure to environmental and occupational nephrotoxicants is not commonly considered in this regard. However, chronic, high-level lead exposure, that is, blood lead levels persistently above 70–80 μg/dl, is an established risk factor for CKD. This has been documented in long-term follow-up of children in the Queensland, Australia lead poisoning epidemic,[10] mortality studies of lead exposed workers,[11] historical occupational experience,[12] and animal models.[13] At this level of exposure, lead is generally the primary cause of renal pathology, which is characterized by chronic tubulointerstitial nephritis and diagnosed as lead nephropathy.[14] Fortunately, exposure at these levels is increasingly rare, particularly in developed countries. The geometric mean blood lead level in adults declined from 13.1 μg/dl in the National Health and Nutrition Examination Survey II, conducted between 1976–1980,[15] to 1.56 μg/dl in the most recent survey conducted between 2001 and 2002.[16] Similarly, occupational lead exposure in industrialized countries, although much higher than environmental exposure, is well below historic levels associated with lead nephropathy.

In this review, we consider whether current lower levels of lead exposure continue to contribute to nephrotoxicity. There are a number of reasons for concern in this regard. Globally, environmental exposure to lead is ubiquitous. Lead is stored in bone resulting in ongoing endogenous exposure. Body burdens of such cumulative toxicants tend to increase with age as does risk for renal disease from other factors. In addition, despite the overall decline in exposure, certain populations, even in developed countries, continue to experience higher lead exposure.[17,18] These include inner city children and adults of lower socioeconomic status, particularly African-Americans who, as noted above, also have a higher prevalence of end-stage renal disease. Occupational settings of particular concern include small and/or mobile workplaces, such as radiator repair shops and construction sites. Children continue to be exposed from lead paint. Many other sources of lead exposure have been identified, such as children's jewelry,[19] folk remedies, glazed pottery, and even candy.[20] Recently, attention has focused on urban water as a continued source of lead exposure.[21,22] Internationally, blood lead levels are higher in developing countries owing to continued use or later phase-out of leaded gasoline and paint.[23,24] Occupational exposure in these countries is higher as well.

In order to review recent research of relevance for the question of lead-related nephrotoxicity at current exposure levels, we have categorized the literature by study population as strengths, weaknesses, and conclusions that can be made are different in each setting. Several lead dose measures are used in this body of literature. Blood lead is a short-term measure (half-life of 30 days[25]) that reflects exposure from current exogenous sources and the release of endogenous lead from bone. Bone lead is a cumulative dose measure that also provides information on potential for endogenous exposure.[25,26] Lead in trabecular bone (commonly measured in the patella or calcaneus) is more bioavailable than lead in cortical bone (measured in the mid-tibia) and has a shorter half-life (estimated at 1–16 years compared to 10–30 years for cortical bone.[25,27] Chelatable lead is thought to represent a bioavailable pool of lead from blood, soft tissue, and bone. Calcium disodium ethylenediaminetetraacetic acid (EDTA) has traditionally been used for chelation; dimercaptosuccinic acid (Succimer) is a more recent option.

LITERATURE SEARCH STRATEGY

We searched MEDLINE for studies involving the effect of lead on the kidney in humans using the following terms: lead and (occupational, environmental, or exposure) and (kidney, renal or nephrotoxicity). Limits included human and English language. The time period covered 1 January 1985–31 December 2005 to include the initial general population studies on the topic. An additional search for general population studies was conducted using the same search terms and time period in an Embase search, which was limited to humans but had no language limits.

Pertinent earlier papers from the investigators' files were discussed when relevant. We manually reviewed cited references from identified articles. Owing to the heterogeneous populations studied, small number of publications in general populations, and the range of renal outcomes analyzed, no attempt to pool data quantitatively was made. Therefore, studies were not excluded *per se*. However, studies that incorporated stronger designs and analyzed renal outcomes of known prognostic value were emphasized.

GENERAL POPULATION STUDIES

We identified 17 publications within the past two decades that have evaluated the effect of environmental lead exposure on renal function in adult general populations.[17,28–43] In six publications, early biological effect markers were the only renal outcome measures analyzed.[38–43] Determining the clinical relevance of these results is difficult owing to the limited number of prospective studies documenting the prognostic value of these markers in lead exposed populations. Therefore, the 11 studies that analyzed clinical renal outcomes (blood urea nitrogen, serum creatinine, measured and/or estimated creatinine clearance, and/or estimated glomerular filtration rate (GFR)) were summarized (Table 1). These publications included eight populations, primarily in the US and Europe. Four publications addressed different time points or lead dose measures in the same longitudinal study (Normative Aging Study). Statistically significant associations between higher lead dose and worse renal function were observed in nine publications (representing six different populations). Associations between blood lead and creatinine-based renal outcomes were the most commonly reported.[17,29–31,33,35,36] Results in longitudinal data were consistent with those observed cross-sectionally, although significant associations were limited to susceptible populations (diabetics and hypertensives) in one study.[33] Hypertensives also emerged as a susceptible group in National Health and Nutrition Examination Survey data.[35] Both studies that measured bone lead reported associations not observed with blood lead, suggesting that assessment of cumulative lead dose is important in understanding lead-related nephrotoxicity.[32,33] A review of the two studies in which no significant associations were observed is notable for the fact that one is limited by small sample size and minimal statistical analysis.[37]

Overall, these studies have a number of strengths including assessment of a range of lead dose measures and renal outcomes; statistical analysis that adjusted for numerous renal risk factors and, in two, evaluated longitudinal data;[31,33] and generally large sample sizes. The analyses of National Health and Nutrition Examination Survey data have the advantage of being representative of the US non-institutionalized, civilian population.[17,35] The general consistency of the results provides important evidence that lead-related nephrotoxicity remains a public health concern, particularly in susceptible populations.

Table 1 | Research on the renal effects of lead exposure in general populations[a]

Reference and study location	Study population; date; sample size; % male	Mean (s.d. or range) Age (years) Blood lead (μg/dl)	Study design	Statistical modeling; covariates	Adjusted β coefficients (95% CI) for observed associations
Longitudinal studies					
Kim et al.[31] Boston, MA, USA	Normative Aging Study; 1979–1994; 459; 100%	At baseline: 56.9 (37.7–87.5) years 9.9 (6.1) μg/dl	Longitudinal and cross-sectional analysis of data from examinations conducted every 3–5 years; Exclusionary criteria not specified	Random effects Baseline age, time since initial visit, body mass index, smoking status, alcohol ingestion, education level, hypertension, and in longitudinal analysis, serum creatinine at the beginning of the follow-up interval and time between evaluations	*Longitudinal analysis* Log-transformed blood lead and change in serum creatinine over subsequent follow-up period in: All participants (*P*=0.07) 0.02 (−0.004, 0.044) 428 whose peak blood lead was ⩽25 μg/dl 0.027 (0.0, 0.054) *Cross-sectional analysis* Log-transformed blood lead and concurrent serum creatinine in: All participants 0.033 (0.009, 0.057) 141 whose peak blood lead was ⩽10 μg/dl 0.06 (0.023, 0.097) 10-fold higher blood lead level associated with 0.08 (95% CI: 0.02, 0.13) mg/dl higher concurrent serum creatinine and a 0.05 (95% CI: −0.01, 0.10) mg/dl greater change in serum creatinine over the subsequent follow-up interval in all participants after adjustment
Tsaih et al.[33] Boston, MA, USA	Normative Aging Study; 1991 to ∼2001; 448; 100%	At baseline: 66.0 (6.6) years; 6.5 (4.2) μg/dl	Longitudinal and cross-sectional analysis of data from two evaluations over a mean 6-year period Six (*n*=26) and 26% of subjects had diabetes and hypertension, at baseline, respectively Tibia and patella lead also measured Exclusionary criteria=no follow-up in 259; serum creatinine, lead dose, and key covariates not statistically different at baseline between those with and without follow-up	Multiple linear regression, interaction models Age, age squared, body mass index, diabetes, hypertension, smoking status, alcohol consumption, analgesic, and diuretic use, and in longitudinal analyses, baseline serum creatinine and its square	*Longitudinal analysis* Baseline lead dose not associated with change in creatinine in all 448. 0.009 (−0.001, 0.019) (for natural ln-transformed blood lead) Significant interaction of ln baseline blood and tibia lead with diabetes in models of annual change in serum creatinine. For ln blood lead: 0.076 (0.031, 0.121) in diabetics 0.006 (−0.004, 0.016) in non-diabetics Interaction also noted in hypertensive participants with tibia lead, although the diabetics likely present in this group may have been influential there as well. *Cross-sectional analysis* No significant associations between lead dose and concurrent serum creatinine at baseline in all 448; ln-transformed tibia lead associated with serum creatinine in diabetics. One of three associations at follow-up significant: natural ln-transformed blood lead with concurrent serum creatinine 0.149 (0.041, 0.257)
Cross-sectional studies: Renal outcomes include estimated/measured creatinine clearance and/or estimated GFR					
Akesson et al.[36] Sweden	Women's Health in the Lund Area Study; 1999–2000; 820; 0%	Medians: 58 (53–64) years 2.2 (1.1–4.6 (5th and 95th %)) μg/dl	Exclusionary criteria=renal cancer (*n*=1) and lithium treatment (*n*=3)	Multiple linear regression Age, body mass index, diabetes, hypertension, and regular use of nephrotoxic drug, blood, and urinary cadmium (in separate models), smoking status (by stratification)	Blood lead (μg/dl) with GFR (ml/min) estimated from cystatin C:[44] –2.0 (−3.2, −0.9) Blood lead (μg/dl) with estimated creatinine clearance[b] (ml/min): –1.8 (−3.0, −0.7)
Muntner et al.[35] US	NHANES III; 1988–1994; Study population representative of US non-institutionalized,	Age reported categorically 4.21 (0.14) μg/dl (hypertensives) 3.30 (0.10) μg/dl (normotensives)	Renal outcomes=elevated serum creatinine (defined as ⩾99th percentile of each race–gender-specific distribution for participants aged 20–39 years without	Multiple logistic regression Age, race, gender, diabetes, systolic blood pressure, smoking	Odds ratios for both renal outcomes increased by quartile of blood lead among hypertensives but not normotensives. Odds ratios for CKD in hypertensives after adjustment:

Table 1 | Continued

Reference and study location	Study population; date; sample size; % male	Mean (s.d. or range) Age (years) Blood lead (µg/dl)	Study design	Statistical modeling; covariates	Adjusted β coefficients (95% CI) for observed associations
	civilian population; 15 211 (4813 hypertensives); 48%		hypertension or diabetes) and CKD (defined as estimated GFR[c] < 60 ml/min/1.73 m²) Exclusionary criteria not specified; data from 13 141 of 18 825 adults used in final models	status, history of cardiovascular disease, body mass index, alcohol consumption, household income, education level, marital status, and health insurance	*Blood lead* / *%* / *Odds ratio (95% CI)* Quartile 1 (0.7–2.4) / 6.1 / 1.00 Quartile 2 (2.5–3.8) / 10.4 / 1.44 (1.00, 2.09) Quartile 3 (3.9–5.9) / 10.8 / 1.85 (1.32, 2.59) Quartile 4 (6.0–56.0) / 14.1 / 2.60 (1.52, 4.45) $P < 0.001$ for χ^2 test for trend Twofold higher blood lead associated with odds ratio for CKD of 1.38 (95% CI: 1.15, 1.66) in hypertensives after adjustment In normotensives, higher blood lead was associated with a higher prevalence of CKD in diabetics
Muntner et al.[17] US	NHANES 1999–2002; 9961; gender not reported	Age not reported Geometric mean (95% CI) 1.64 (1.59, 1.68) µg/dl	CKD (defined as estimated GFR[c] < 60 ml/min/1.73 m²) Exclusionary criteria not specified	Multiple logistic regression Age, race/ethnicity, gender, diabetes, smoking status, alcohol, body mass index, education, and health insurance	Odds ratios for CKD in all increased by quartile of blood lead, significant χ^2 test for trend
Payton et al.[30] Boston, MA, USA	Normative Aging Study; 1988–1991; 744; 100%	64.0 (7.4) years; 8.1 (3.9) µg/dl	Exclusionary criteria = missing data present in 251	Multiple linear regression Age, body mass index, analgesic & diuretic use, alcohol consumption, smoking status, systolic/diastolic blood pressure	Log transformed (ln) blood lead with ln 24-h measured creatinine clearance −0.04 (−0.079, −0.001) After adjustment, a 10 µg/dl higher ln blood lead was associated with a 10.4 ml/min lower ln creatinine clearance. A 10-fold increase in blood lead associated with 9% decrease in creatinine clearance (as noted by Kim et al.[31]) Borderline significant ($P < 0.1$) associations between ln blood lead and both serum creatinine ($\beta = 0.027$) and ln estimated creatinine clearance[b] ($\beta = 0.022$)
Staessen et al.[29] Belgium	Cadmibel study; 1985–1989; general Belgian population in four cadmium polluted and unpolluted areas; 1981; 48.7%	48 (16) years Geometric mean Males: 11.4 (2.3–72.5) µg/dl Females: 7.5 (1.7–60.3) µg/dl	Exclusionary criteria = missing data present in 302; potentially inaccurate 24 h urine collections in 44	Multiple linear regression Age, age squared, gender (by stratifying), body mass index, blood pressure, ferritin level, smoking status, alcohol ingestion, rural vs urban residence, analgesic and diuretic use, blood, and urinary cadmium, diabetes, occupational exposure to heavy metals, and gamma glutamyl transpeptidase	Log transformed blood lead with 24 h measured creatinine clearance −9.5 (−18.1, −0.9) in males −12.6 (−20.3, −5.0) in females 10-fold higher blood lead associated with 10 and 13 ml/min lower measured creatinine clearance in men and women, respectively Log-transformed blood lead also negatively associated with estimated creatinine clearance[b] but not significantly associated with serum creatinine
Wu et al.[32] Boston, MA, USA	Normative Aging Study, 1991–1995 709; 100%	67.0 (7.4) years 6.2 (4.1) µg/dl	Tibia and patella lead also measured Exclusionary criteria not specified	Multiple linear regression Age, body mass index, hypertension, smoking status, alcohol ingestion, analgesic medication use	Significant negative association between patella lead and estimated creatinine clearance[b]: $\beta = -0.069$; $P = 0.02$ (neither s.e. nor CI provided) Borderline significant ($P = 0.08$) negative association between tibia lead and creatinine clearance. No lead measure was significantly associated with serum creatinine; no blood lead associations were significant
Cross-sectional studies: Other clinical renal outcomes					
De Burbure et al.[34] France	399 adults who lived ≥ 8 years near two nonferrous smelters; 50% males	Means ranged from 34.6 (8.9) years (exposed males) to 35.9 (9.6) years (exposed females)	Exclusionary criteria included pregnancy, cancer, diabetes, kidney disease, occupational smelter	Multiple linear regression Age, sex, body mass	No significant difference in mean serum creatinine between exposed and unexposed groups. After adjustment for covariates, log-transformed blood lead not significantly

Table 1 | Continued

Reference and study location	Study population; date; sample size; % male	Mean (s.d. or range) Age (years) Blood lead (μg/dl)	Study design	Statistical modeling; covariates	Adjusted β coefficients (95% CI) for observed associations
	201 age- and gender-matched controls Date not provided (Note – only results in adults presented herein)	Geometric means ranged from 4.2 (0.2) μg/dl (control females) to 7.1 (0.18) μg/dl (control males)	exposure, recent dental work, and missing data. Numbers excluded not stated, however, serum creatinine data reported in 479 of original 600	index, area of residence, smoking, alcohol ingestion, log urine mercury, log blood cadmium and urinary creatinine	associated with serum creatinine (data not presented in publication).
Mortada et al.[37] Egypt	Not applicable – details of population recruitment not provided; date not provided 68; 100%	30 (25–35) years (smokers) 31.8 (25–38) years (non-smokers) 14.4 (3.4) μg/dl (smokers) 10.2 (3.1) μg/dl (non-smokers)	Also measured cadmium, and mercury in blood and all three metals in urine, hair, and nails. Exclusionary criteria=occupational exposure to any of the three metals, dental amalgams, drug intake, diabetes, hypertension, and hepatic, renal or urological disease. Smokers and non-smokers matched on socioeconomic status.	t-test for independent samples; Spearman correlation	No significant difference in serum creatinine or BUN by smoking status (blood lead levels significantly higher in smokers as compared to non-smokers). No significant correlations of any of the four lead measures with renal outcomes (only assessed in 35 smokers; data not presented in publication)
Pocock et al.[28] Britain	British Regional Heart Study; year not provided; 7364; 100%	Mean not reported, range 40–59 years Mean blood lead not reported	Exclusionary criteria not specified	Correlation; analysis of covariance adjusting for alcohol	Correlations of blood lead with log transformed serum creatinine, urate, and log urea=0.00, +0.1, −0.08 (unadjusted data) (P<0.001 for urate and urea) Partial correlations for urate and urea after adjustment for alcohol=+0.06 and −0.05 (P-values not reported)

BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey.
[a]Studies in adult general populations published in the last 25 years in which relations between lead dose and clinical renal outcomes (BUN, serum creatinine, measured or estimated creatinine clearance, or estimated GFR) were analyzed.
[b]Creatinine clearance estimated using the Cockcroft–Gault equation.[45]
[c]GFR estimated by the abbreviated Modification of Diet in Renal Disease (MDRD) equation.[46]

OCCUPATIONAL POPULATION STUDIES

Research on renal outcomes from occupational lead exposure is categorized by reported results (Table 2). Compared to the work described above in general populations, this body of literature is larger, however, the results are less consistent. This is puzzling as most dose–response relations are linear. Biologically, lead dose consistent with occupational exposure (i.e., blood lead levels between 20 and 50 μg/dl) should be nephrotoxic if lower (<10 μg/dl) and higher (>80 μg/dl) doses are. A number of factors may be involved in this seeming paradox. Some are unique to the occupational literature. These studies generally have small sample sizes, resulting in less power to detect significant differences. Most are cross-sectional studies of currently employed workers, a group that is well known to be healthier than the general population (the healthy worker effect). Lead workers who are followed in a medical surveillance program (a common practice) are often removed from exposure if renal function decline is observed. This may result in removal from the workplace, yet few studies have included former workers. In many studies, exclusionary criteria for a range of diseases, such as HTN and diabetes, were applied. The number of workers subsequently excluded was not always reported, making it difficult to determine if the healthy worker effect

was substantially increased. Statistical analyses were more limited than in general population studies. Analyses limited to comparisons of crude mean outcomes between exposed and control workers are problematic, when lead levels in the latter group are in the range associated with adverse renal outcomes in the general population. Limited lead exposure assessment may also be a factor, as few studies have included cumulative measures of lead dose and blood lead varies more owing to external exposure in the occupational setting. Other limitations that are pertinent for research on the adverse renal effects of lead exposure in any population include insensitivity of the clinical renal outcomes and the lack of uniformly accepted early markers of renal damage in lead exposure. As discussed below, coexposure to environmental cadmium may also account for differences in reported associations between studies, particularly for N-acetyl-β-D-glucosaminidase (NAG). In general, these limitations result in bias towards the null meaning that actual associations are obscured.

Finally, one factor that has received relatively little attention to date involves the paradoxical inverse associations observed in some studies (Table 2; Category 4). These unexpected associations have been reported with blood, tibia, and dimercaptosuccinic acid-chelatable lead in the

Table 2 | Research on the renal effects of occupational lead exposure[a]

Significant results	Details and examples	References
Mean difference in one or more measures of clinical renal function[b] between lead workers and control group and/or positive association(s) between higher lead dose and worse clinical renal function	Traditional pattern of lead-related nephrotoxicity. Mean serum creatinine higher in exposed compared to control workers. Higher blood or bone lead associated with higher serum creatinine in all workers.	47–57
Mean difference or association for renal biomarkers[c]; clinical outcomes not assessed	Relatively recent approach to lead-related nephrotoxicity to address issue of insensitivity of clinical renal measures. Higher blood lead associated with higher RBP	58–66
Significant results for renal biomarkers but not clinical outcomes	Higher blood lead associated with higher RBP but not serum creatinine	67–78
Paradoxical associations with higher mean creatinine clearance in the lead exposed group and/or inverse associations between higher lead dose and worse clinical renal function	May indicate lead-related hyperfiltration. Higher lead dose associated with lower BUN and serum creatinine and/or higher creatinine clearance	47,57,79,80,81
None[d]		82–86

BUN, blood urea nitrogen; RBP, retinol-binding protein.
[a]Published between 1985–2005, adult populations.
[b]Clinical renal function defined as BUN, serum creatinine, estimated and/or measured creatinine clearances, and/or estimated GFR.
[c]Renal biomarkers examples include N-acetyl-β-D-glucosaminidase, RBP, β_2 microglobulin, and α_1-microglobulin.
[d]Interestingly, one of these studies[85] included two workers with high lead dose and lower creatinine clearance who had biopsy evidence of chronic interstitial nephritis, thus a pattern consistent with lead nephropathy. In another, the association was no longer significant after the removal of two participants with abnormal renal function that appear to be outliers.[86]

occupational setting and with blood lead in a recent study of environmentally exposed children.[87] Higher mean creatinine clearance compared to controls was also observed in one study of adults who were previously lead poisoned as children.[88] Although observed renal function was not consistently in a supranormal range, these associations may indicate a lead-related hyperfiltration process. Data from lead workers in South Korea suggest a temporal pattern that is consistent with hyperfiltration.[47] Inverse associations (i.e., higher lead dose associated with lower serum creatinine) were noted in younger workers; however, the opposite was observed in older workers (i.e., higher lead dose associated with higher serum creatinine). Two longitudinal studies in rats are critical to our understanding of this process in lead exposure. High exposure animals had mean blood lead levels of ~ 50, 90 and 125 µg/dl at 1, 3, and 6 months, respectively, at which point lead exposure was reduced and levels declined to ~ 60 µg/dl at 12 months.[13] Lower exposure resulted in mean blood lead levels between ~ 20 and 30 µg/dl throughout.[89] Compared to controls, mean GFR (measured with ^{125}I-iothalamate clearance) was significantly higher at 1 month in the lower exposure animals and in both groups at 3 months. In the high exposure rodents, a positive association between blood lead and GFR was observed in the first 6 months; however, tubulointerstitial fibrosis became apparent at 6 months and GFR was decreased compared to controls at 12 months. Interestingly, despite a similar degree of hyperfiltration initially (and an earlier onset), subsequent renal damage was much less severe in the lower exposed animals.

Whether this process contributes to pathology in human lead exposure remains unclear and will require longitudinal studies. Regardless, significant associations could be obscured if opposite direction associations are present in different segments of the study population and interaction models to address this are not performed. This is a valid concern as the factors involved in these inverse associations in lead exposed populations are not well defined at present.

PATIENT POPULATION STUDIES
Studies in various patient populations have also contributed to the body of knowledge concerning the adverse renal impact of lead. Patients with CKD, gout, and/or HTN have been the focus of this work as risk for these diseases is increased with high-level lead exposure, particularly when two or more coexist in the same patient. Early research focused on lead nephropathy and body burdens were high (> 600 to 650 µg lead excreted in 72 h following chelation with EDTA).[90,91] More recent work has involved patients with earlier stages of CKD and much lower lead body burdens, thus addressing the issue of low-level lead as a cofactor with other renal risk factors in susceptible populations. This work has been published by Lin and co-workers in Taiwan; a discussion of two recent studies serves to illustrate the current state of this research and the different approaches they use to study this issue. The first approach involves prospective study of susceptible patient populations to determine if renal function decline is greater in participants with higher baseline chelatable lead body burdens. Yu et al.[92] followed 121 CKD patients over a 4-year period. Eligibility criteria included stable renal function (serum creatinine from 1.5 to 3.9 mg/dl), well-controlled blood pressure, cholesterol and daily protein intake, and EDTA-chelatable lead < 600 µg/72 h. Sixty-three patients had 'high-normal' EDTA-chelatable lead levels (⩾ 80 but < 600 µg/72 h);

58 patients had 'low-normal' EDTA-chelatable lead levels ($<80\,\mu g$ lead/72 h). Mean blood lead was higher in the former group (4.9 vs 3.4 $\mu g/dl$). The groups were similar in most other baseline risk factors. However, borderline statistically significant ($P<0.1$) differences were present (older age and chronic glomerulonephritis more prevalent in the 'high-normal' lead group chronic interstitial nephritis and hypertensive nephropathy less prevalent). Fifteen patients in the 'high-normal' chelatable lead group reached the primary end point (doubling of serum creatinine or need for hemodialysis) compared to only two in the 'low-normal' group ($P=0.001$).

Associations between baseline chelatable or blood lead levels and change in GFR were modeled separately using generalized estimating equations. Based on these models, 10 $\mu g/72$ h higher chelatable lead and 1 $\mu g/dl$ higher blood lead were associated with a reduction in GFR of 1.3 and 4.0 ml/min/1.73 m^2, respectively, during the 4-year study period. Given the lead dose ranges in this study, this is a clinically relevant association.

The second approach used by Lin et al., involves randomized EDTA chelation trials to determine if this therapy changes the rate of renal function decline. Chelation in lead exposure is controversial owing to the potential for it to be used in lieu of exposure reduction. In addition, cases of acute tubular necrosis were reported following early clinical use of EDTA that involved very large doses.[93] However, adverse renal effects have not been observed in subsequent work using lower doses.[91,93] In their largest chelation trial to date, Lin et al.[94] randomized 64 patients whose EDTA-chelatable lead levels were 80–600 $\mu g/72$ h; half received weekly chelation with 1 g EDTA intravenously for up to 3 months (mean 5 weeks) and half received a weekly placebo infusion for 5 weeks. Renal risk factors were similar in the two groups. Mean blood lead levels were 6.1 and 5.9 $\mu g/dl$ in treated and control groups, respectively. In the subsequent 24 months, chelation was repeated in 19 (59%) participants owing to increases in serum creatinine in association with rebound increases in chelatable lead levels. Each received one additional chelation series (mean of four weekly infusions), a mean of 13.7 months after the first chelation period. At the end of the 2-year study period, mean estimated GFR increased by 2.1 ml/min/1.73 m^2 in the chelated group compared to a decline of 6.0 ml/min/1.73 m^2 in the controls ($P<0.01$). Benefits from chelation have also been observed in rodent models of lead-related nephrotoxicity.[95–97] This did not appear to occur via reversal of structural damage;[97] improved hemodynamics from reduction of reactive oxidant species may be a mechanism.[98] It is also important to note that chelation may have a direct beneficial effect on kidney function, irregardless of lead exposure. Dimercaptosuccinic acid has been reported to prevent renal damage when coadministered during induction of nephrosclerosis in a non-lead-exposed rat model.[98]

The unique body of work by Lin et al., (which also includes work in patient populations with gout and HTN not discussed herein) has numerous strengths including prospective study design, randomization, lead dose assessment that includes bioavailable body burden, longitudinal statistical analysis, and control for multiple renal risk factors. However, to date, this work has been performed in small groups at one clinical center and thus the generalizability of the results to broader populations is unknown. In addition, the observed effect of lead on decline in GFR has been variable. In an earlier study of 202 patients, an increase of 10 $\mu g/72$ h in baseline EDTA-chelatable lead was associated with a decline in GFR of 0.03 ml/min/1.73 m^2 over a 2-year observation period.[94] When adjusted for the shorter follow-up period, this effect, although statistically significant ($P<0.001$), is 20-fold lower than in the most recent work discussed above.[92] Small sample sizes and differences in renal diagnoses between groups may be factors in this variability.

Although preliminary, this line of research could yield important public health benefits if confirmed in large populations (and shown not to worsen cognition). This would indicate that lead body burden contributes to worsening renal function in populations with CKD from a range of causes at much lower levels than previously recognized. Therapeutic options would be available for high-risk patients, who, despite reductions in lead exposure, still experience lead-related nephrotoxicity.

ADDITIONAL CONSIDERATIONS

A number of additional issues may be relevant in assessing the adverse renal impact of lead exposure. However, data are currently too limited to merit in depth discussion. Such areas include the potential for lead-related nephrotoxicity in children, genetic susceptibility, and coexposures, of which cadmium is the most important. Lead-poisoned children who are not chelated are at increased risk for nephropathy as young adults.[10] Recent work in children exposed at lower levels has generally relied on renal biomarkers for outcome assessment. As discussed above, few prospective studies documenting the prognostic value of these markers in lead exposure have been published. Further, some data suggest that renal biomarker levels may decrease post-puberty,[99] so prospective biomarker studies specifically in lead exposed children will be needed to interpret the existing literature. However, two recent publications deserve comment. A positive association between blood lead and serum cystatin C was observed in 200 Belgian adolescents.[100] In 600 European children, higher blood lead was associated with lower serum creatinine and cystatin C,[87] in models that adjusted for age, gender, body mass index, and either blood or urine cadmium (A. Bernard, e-mail communication). Prospective studies of renal function in lead-exposed children are needed to understand the clinical significance of these findings.

Research in the past two decades suggests that certain genetic polymorphisms affect lead toxicokinetics (i.e., modify the relation between lead exposure and internal dose).

The gene that encodes for δ-aminolevulinic acid dehydratase has received most attention in this regard to date. Overall, current data suggest that tighter binding of lead by the isoenzymes of the variant δ-aminolevulinic acid dehydratase[2] allele leads to higher blood lead levels and decreased lead sequestration in bone.[101,79,102] Data to determine whether the δ-aminolevulinic acid dehydratase polymorphism confers additional toxicodynamic risk for the kidney are still quite limited, but are suggestive of an increased risk in lead-exposed populations with the variant allele.[32,79,102–104]

Finally, exposure to other environmental nephrotoxicants may affect risk. Cadmium is likely to be the most important in this regard as this metal has many similarities to lead. It is also a cumulative toxicant that is stored long term in the body. Environmental cadmium exposure in the US occurs primarily through food and smoking.[105] The existing data indicate that cadmium exposure, at levels common in the US, confounds associations between lead exposure and at least one renal outcome, NAG. Studies have reported higher mean NAG in lead workers compared to controls; however, NAG was correlated with urinary cadmium (CdU; a cumulative measure of exposure) rather than lead dose.[80,67] CdU was associated with the NAG-B isoenzyme (released with breakdown of proximal tubular cells) even at CdU levels $< 2 \mu g/g$ creatinine.[106] In Korean lead workers, both CdU and tibia lead were positively associated with NAG[47]. However, a $0.5 \mu g/g$ creatinine increase in cadmium had the same effect on NAG as a $66.9 \mu g$ lead/g bone mineral. The fact that mean CdU was $1.1 \mu g/g$ creatinine, indicating environmental rather than occupational exposure, again illustrates the impact of cadmium on NAG.

Lower level cadmium exposure may also confound or modify relations between lead exposure and clinical renal outcomes, although the data are too limited to draw firm conclusions. Occupational cadmium exposure increases the risk for clinical renal dysfunction,[107,108] as does high-level environmental exposure.[109,110] However, most recent studies of lower level cadmium exposure are cross-sectional and have assessed renal biomarkers, rather than clinical renal outcomes.[43,111–113] Two recent exceptions include a report of increased renal dialysis and transplantation rates in residents of cadmium-polluted areas in Sweden[114] and associations of higher blood lead and blood and CdU with lower estimated creatinine clearance and GFR in Swedish women.[36] However, as noted above, higher blood lead was associated with lower creatinine clearance in the Cadmibel study whereas urinary and blood cadmium were not.[29] Additional studies assessing both lead and cadmium are needed.

CONCLUSIONS

The research reviewed herein utilized a variety of study approaches in different populations. Overall, these diverse lines of evidence indicate that lead exposure, at much lower levels than those causing lead nephropathy, acts as a cofactor with more established renal risk factors to increase the risk for CKD and the rate of progression. Adverse renal effects

have been reported at mean blood lead levels $< 5 \mu g/dl$. Cumulative lead dose was also associated with worse renal function. The data available to date are not sufficient to determine whether current blood lead level or cumulative exposure with higher past blood lead levels is the more important determinant of nephrotoxicity. However, Kim *et al.*[31] noted associations in participants whose peak blood lead levels, dating back to 1979, were $\leqslant 10 \mu g/dl$. Populations with diabetes, HTN, and/or CKD appear to be at greater risk for adverse renal effects from lead. Moreover, recent research suggests that the adverse impact of lead on renal function decline in CKD from a range of causes may be reduced with chelation, even at lead body burdens previously considered normal. Although preliminary, this line of research deserves further study as it could yield important public health benefits if confirmed in large populations.

Residual confounding is unlikely to explain associations between lead exposure and renal function. Muntner *et al.*[35] observed that the odds ratios for both renal outcomes assessed in hypertensives, initially adjusted for age, race, and gender, actually increased slightly following additional adjustment for a range of covariates including diabetes, blood pressure, smoking, cardiovascular disease, body mass index, alcohol, and socioeconomic status indicators. Furthermore, most studies adjusted for blood pressure, which is likely to be in the causal pathway and thus may result in an underestimate of effect. Reverse causality, which attributes increased lead dose in general population studies to reduced lead excretion as a consequence of renal insufficiency, is also not likely to be a major explanatory factor. Longitudinal data indicate that lead dose at baseline is associated with subsequent decline in renal function. Furthermore, associations in the Normative Aging Study population occurred over the entire serum creatinine range,[31] and persisted when data from participants with serum creatinine $> 1.5 mg/dl$ were removed.[33] The impact of publication bias is always difficult to assess. A type of publication bias is present in the reviewed studies that reported no significant associations but did not show the data. In addition, at least one cadmium study appears to include unpublished longitudinal lead data.[115] However, no other evidence of unpublished data on associations between lead dose and renal function in general populations was identified through the MEDLINE and Embase search strategies used or in population descriptions and references of reviewed papers.

Inverse associations between higher lead dose and worse renal function may be mediated through a hyperfiltration mechanism. Although potentially of mechanistic importance, a more immediate concern is the fact that, if interaction is not specifically explored in data analysis, risk may be underestimated. The potential for such underestimation in lead workers, along with new knowledge regarding susceptible populations, indicates that lead exposure in workers must be controlled not simply to reduce risk for lead nephropathy but also to minimize steeper renal function decline with aging as other cofactors develop. Monitoring of

cumulative lead dose may be important in this effort. Given these limitations, current permissible exposure levels[116,117] may not be as protective for lead workers as previously thought. Finally, there are a number of data gaps, in terms of effects in children, genetic susceptiblity factors, and co-exposures, which require further study.

Globally, despite substantial reductions in lead exposure overall, two risk groups for lead-related nephrotoxicity remain: (1) those with higher exposure levels still common in developing countries and in minority populations in developed countries and (2) those with other renal risk factors. From a public health perspective, certain groups, such as those of lower socioeconomic status, are at highest risk as they have higher lead exposure and prevalence of diseases that increase susceptibility. Ultimately, the global public health impact may be most significant in developing countries where obesity, and secondary HTN and diabetes mellitus, are increasing more rapidly than lead exposure is declining. Continued global efforts to reduce lead exposure are obviously important; technology transfer is critical to reduce associated costs. Given the increasing prevalence of renal disease, research to better delineate the contribution made by lead exposure and to determine whether chelation is beneficial is also needed.

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