Journal of
Toxicology and Risk Assessment

Research Article: Open Access

Long-Term Effects on Renal Function in Children and Adolescents Due to Environmental Exposure to Lead-Results from an 11-Year Prospective Cohort Study

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Abstract

Context: Most studies associating low-level lead exposure and kidney function have been carried out in adults and only a few studies have examined this relation in healthy children, adolescents, or young adults.

Objective: To evaluate the long-term effects on renal functions due to environmental lead exposure in a cohort of children and adolescents that are permanent inhabitants of the three most polluted residential developments by lead in Torreon, Coahuila, Mexico.

Materials and Methods: The biochemical markers of renal function, estimated glomerular filtration rate (eGFR), as well as, blood lead levels, were measured in a cohort of 480 children and adolescents. According with the blood lead levels (BLLs), subjects were grouped in three exposure categories (Category I: < 25 µg/dL; Category II: > 25 - < 45 µg/dL and Category III: > 45 µg/dL).

Results: The mean baseline, highest and last BLLs in the assessed population, was 15.5, 17.2 and 3.3 µg/dL, respectively. The average quantity of serum urea, creatinine, uric acid levels, and eGFR were similar between the exposure categories; however the frequency of abnormal l uric acid level was significantly higher in the two most exposed categories ($p < 0.01$). In the multivariate statistical model, the frequency of abnormal serum creatinine concentration was positively linked with uric acid, while the frequency of abnormal uric acid was negatively associated with years of work, and, finally, there was a negative correlation between the eGFR and creatinine levels. No significant association was found between BLLs with the biochemical markers of the kidney functions or with the eGFR.

Conclusion: Our data indicated that there was not a relevant relation between the BLLs with the biochemical markers of renal functions or with the eGFR in this cohort of healthy infants and juveniles environmentally exposed to lead.

Keywords

Blood lead levels, Renal function, Creatinine, Uric acid, BUN, Glomerular filtration rate.

Introduction

Lead is a widespread toxicant with well-established detrimental health effects [1]. Environmental exposure to lead occurs through different means such as industrial and combustion sources, lead paint, folk remedies, glazed pottery, and sometimes by drinking water. Some groups are disproportionately exposed to lead, including those who live close to industrial facilities or with low socio economic status and workers in small or mobile workplaces such as radiator repair shops and construction sites [2]. Over the last decades, there has been a remarkable reduction in environmental sources of lead, improved protection from occupational lead exposure, and an overall decreasing trend in the prevalence of elevated BLLs in U.S. adults [3]. However, current research continues to find that BLLs previously considered harmless can have harmful effects in adults, such as a decreased renal function and an increased risk for hypertension at BLLs < 10 µg/dL [4,5].

Several epidemiologic studies showed a strong relationship between BLLs and a decline in renal function associated with age (study done with populations not occupationally exposed) [6-9]. In these studies, significant correlations exist between BLLs < 10 µg/dL and elevations in serum creatinine; for every 10-fold increase in blood lead, serum creatinine increased 0.14 mg/dL.

Lead, like other heavy metals (mercury, cadmium, arsenic), has toxic effects on renal tubular function causing uric acid retention, and toxic levels above 80 µg/dL are linked with deteriorated kidney function [10].

Lead nephropathy has been well documented in occupationally exposed workers. It manifests as: proximal tubular damage, glomerular sclerosis, interstitial fibrosis, and among symptoms: proteinuria, impaired transport of glucose and organic anions, and lowered glomerular filtration rate (GFR) [11].

Most studies of low-level lead exposure (BLL < 10 µg/dL) and

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Citation: Recio-Vega R, Gurrola-Mendez A, Valdez-Abrego C, Rivera-Guillen M (2015) Long-Term Effects on Renal Function in Children and Adolescents Due to Environmental Exposure to Lead-Results from an 11-Year Prospective Cohort Study. J Toxicol Risk Assess 1:003

Received: November 19, 2015: **Accepted:** December 29, 2015: **Published:** December 31, 2015

kidney function examined adults at a mean age of 50 years and older with a high prevalence of comorbid conditions and kidney disease risk factors, such as diabetes mellitus, hypertension, and smoking [12]. Few studies have assessed the association between low-level lead exposure and kidney function in infants and adolescents, who are generally free from these comorbidities [12,13].

Chronic nephropathy, subsequent to childhood lead poisoning, has been reported from Queensland, Australia [12].

The aim of the present longitudinal study was to evaluate lead's long-term effects on renal function in a cohort of children and juveniles that are permanent inhabitants of the three most historical polluted residential developments that are located within 2 km of the biggest Latin-America smelter.

Materials and Methods

Study design and subjects

We performed a longitudinal cohort study with subjects aged (at present) 15 - 45 years who were enrolled since childhood/adolescence in the Childhood Blood Lead Level Surveillance Program by Coahuila's Ministry of Health [14]. Data from this program was employed as the basis of the investigation. The database consists of BLL surveillance facts from 1998 to 2015 and includes information from individuals aged 0 - 60 years (> 15,000) that live in the 32 residential developments located around the biggest smelter in Latin America which is located in Torreon, Coahuila, Mexico. According with their BLL, blood samples are taken every 1 (> 25 μg/dL), 3 (10-24.9 μg/dL) or 12 (< 10 μg/dL) months. Potential volunteers were selected by a random sampling method. The permanent inhabitants of the three closer residential developments to the smelter, and in which the highest mean BLL has been registered in their dwellers during the last 25 years, were invited to participate in the study via home visits. Only those participants that fulfilled the recruitment criteria (healthy volunteers and permanent occupants that have lived at least 11 years in the selected residential zones) and those who had not presented any of the exclusion criteria at the time of the study (known or suspected: renal insufficiency, urinary tract infection, hypercalcaemia, or drug-induced nephrotoxic effects; systemic diseases such as connective-tissue diseases or diabetes mellitus; use of drugs that might alter the course of renal disease such as nonsteroidal anti-inflammatory agents, steroids, or immunosuppressive drugs; occupational exposure to lead, arterial hypertension and drug allergies) were included in the study. More than 760 subjects satisfied these criteria, however, only 480 provided the biological samples and completed the questionnaire (participation rate: 71.6%). The evaluated subjects shared a similar socioeconomic status (monthly household income < 300 dollars). The number of blood samples taken per volunteer ranged from 2 to 53, with a mean of 8.7 (median 5.0).

The research protocol was approved by the Ethics Committee of the School of Medicine at Torreon, University of Coahuila, Mexico, and this work has been carried out in accordance with The Code of Ethics of the World Medical Association Declaration of Helsinki.

Questionnaire application

Information was collected at the time of the study through face to face interviews by trained personnel. It included socio-demographic variables (education, socioeconomic status), lifetime residential history, lifestyle factors (smoking, alcohol consumption, exercise and drugs abuse), occupational history, current medications, medical record, diet and history of several known risk factors for renal failure (mentioned in the exclusion criteria), occupational exposure to lead, arterial hypertension and drug allergies.

Written informed consent was obtained from each participant at the time of interview.

Blood and urinary biochemical parameters and eGFR

After a minimum 8 hour fasting, venous blood samples were gathered from the subjects, glucose, urea nitrogen, creatinine, uric acid, and blood lead concentrations were measured. The serum creatinine level was evaluated by the modified kinetic Jaffe reaction using a Hitachi 737 analyzer (Roche Diagnostics, Indianapolis, Indiana, USA), whereas blood urea nitrogen (BUN) and uric acid using spectrometry and commercial kits. Abnormal serum creatinine, BUN and uric acid levels were defined as serum concentrations higher than 1.20, 50.0 and 7.0 mg/dL, respectively [15]. The estimated glomerular filtration rate (eGFR) (measured in milliliters per minute per 1.73 m^2) was calculated by the abbreviated Modification of Diet in Renal Disease Study (MDRD) formula [16]: $186 \times (\text{Creat} / 88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$ [17]. The Schwartz equation was used to estimate the GFR for teens under age 18: k (height in centimeters)/(serum creatinine in milligrams per deciliter), where k is 0.7 in boys and 0.55 in girls [18]. Impaired kidney function was considered when the serum creatinine overpassed 1.2 mg/dL and the GFR, estimated by MDRD, was below 60 mL/min/1.73m^2. A glomerular filtration rate below 60 mL/min/1.73m^2 represents a decrease of approximately 50% in normal renal function (below this level, it increases the prevalence of complications of chronic kidney disease (CKD) [5,7,18]. Blood zinc protophorphyrin (ZPP) level was measured by directly using a hematofluorometer (ProtoFluor-z, Helena Laboratories, Inc., Beaumont, TX, USA); the normal reference range used was 1-25 μg ZPP/dL.

First urine samples were collected in plastic containers and transported in portable freezers to the laboratory; the samples were assessed the same day for: pH, density, glucose, hemoglobin, ketones, nitrates, proteins and bilirubin using commercial kits. Additionally, urine sediment was evaluated by direct microscopy. Semi quantitative proteinuria was determined using the iChem Velocity urinalysis system (Iris Diagnostics, Beckman Coulter, Krefeld, Germany). The results of the semi quantitative urine protein measurement approximately correlates with albuminuria as follows: + = 0.1 - 0.5 g/L, ++ = 1 g/L - 3 g/L and +++ = > 3 g/L.

Measurement of blood lead level

After a thorough cleaning of the venipuncture area using anti-lead soap and D-wipe towels, 3 mL of whole blood was drawn into a Vacutainer tube (BD Vacutainer Systems, Rutherford, New Jersey). Blood samples were analyzed at the Met-Mex Penoles metals laboratory which has been certified since 2006 for the blood lead analysis by EMA (Entidad Mexicana de Acreditacion). EMA is a National Agency that certifies the Good Laboratory Practices. Graphite furnace atomic absorption spectrophotometry (AAS model 600, with Zeeman Effect background correction: PerkinElmer, Norwalk, CT, USA) was used to measure BLLs according to NOM-199-SSA1-2000 method with the L'vov platform and a matrix modifier. The limit of detection for this method was 0.1μg/dL. The blood lead measurements were calibrated using standards prepared for the lead nitrate (Standard Reference) obtained from the CENAM (Centro Nacional de Metrologia, Mexico). BLLs were measured in duplicate, and the average of the results was used in this analysis.

The intra-and inter-assay coefficients of variation were < 10% and < 15%, respectively. The average intra class correlation coefficient for the duplicates was 0.88 and the average variation at low and high BLLs was ± 1-3 μg/dL (internal and external quality controls were included in each assay). The laboratory participated in three external quality programs (University of Monterrey, Mexico; University of Wisconsin, USA; and the CDC, USA).

The highest BLL was defined as the maximum BLL found in the studied subjects at any time of this study. BLL ≥ 25.0 μg/dL was considered elevated. According to this highest BLL, subjects were divided into four categories: Category I: < 25 μg/dL; Category II: > 25 - < 45 μg/dL; Category III: > 45 - < 70 μg/dL and Category IV: > 70 μg/dL (two subjects had BLL > 70 μg/dL, however, and for statistical analyses, both of them were included into Category III). These BLL Categories are described in the Norma Oficial Mexicana [19]. Since the average BLL and the frequency of subjects in Categories I, II and III were not statistically different between the three selected

Table 1: Socio-demographic, anthropometric characteristics and life style of the participants. Results are shown as arithmetic mean, standard deviation and percentage [median].

	Category I (< 25 µg/dL) (n = 367)	**Category II** (≥ 25 - < 45 µg/dL) (n = 87)	**Category III** (≥ 45 µg/dL) (n = 26)
Age (years)	28.3 ± 8.3 [28.0]	21.0 ± 3.7* [21.0]	18.3 ± 2.5* [17.0]
Gender			
Female	311 84.7%	58 66.6%*	18 69.2%*
Male	56 15.2%	29 33.3%	8 30.7%
BMI	27.2 ± 7.9 [27.0]	25.7 ± 7.5 [25.1]	24.9 ± 9.5 [25.5]
Years of residence	21.9 ± 11.5 [21.6]	19.0 ± 6.1* [19.0]	16.3 ± 5.5* [17.0]
Years of school	11.1 ± 3.33 [11.0]	11.4 ± 3.2 [11.0]	12.3 ± 2.7 [12.0]
Occupation			
Housewife	178 48.5%	27 31.0%*	5 19.2%*
Several[&]	189 51.5%	60 69.0%	21 81.8%
Years of work	5.4 ±10.0 [3.0]	10.8 ± 23.48 [2.0]	1.7 ± 0.44 [2.0]
Occupational exposure to chemical compounds[#]			
Yes	27 7.4%	14 16.1%*	6 15.4%
No	340 92.6%	73 83.9%*	22 84.6%
Smoking			
Yes	94 25.6%	23 26.4%	7 26.9%
No	273 74.3%	64 73.5%	19 73.0%
Alcohol intake			
Yes	198 53.9%	48 55.1%	14 53.8%
No	169 46.0%	39 44.8%	12 46.1%
History of renal diseases			
Yes	101 27.6%	20 23.0%	6 23.1%
No	266 72.4%	67 77.0%	20 76.9%
History of bladder infection			
Yes	55 14.9%	11 12.6%	6 23.0%
No	312 85.0%	76 87.3%	20 76.9%
History of bladder-renal co-infection			
Yes	17 4.6%	3 3.4%	0
No	349 95.3%	84 96.5%	26 100.0%
History of regular analgesic intake®			
Yes	196 53.4%	39 44.8%	16 61.5%
No	171 46.5%	39 44.8%	10 38.4%
History of drug abuse			
Yes	7 1.9%	1 1.1%	0
No	360 98.0%	86 98.8%	26 100.0%
History of lupus			
Yes	5 1.3%	0	0
No	362 98.6%	87 100.0%	26 100.0%
History of diabetes mellitus			
Yes	21 5.7%	4 4.6%	0
No	346 94.2%	83 95.4%	26 100.0%

*$p < 0.05$ Student's t test, or Mann-Whitney test or Chi^2 test (category I vs category II or III).

[&]Office job 30%, self-employed 31.8%, trader 19.6% and student 18.5%.

[#]Organic solvents, heavy metals, welding fumes, pesticides and fertilizers, oil derivate, dust, exhaust smoke, paint and aniline. ® Paracetamol, ibuprofen, salicylates and naproxen were the analgesics exclusively used by participants.

residential areas, the results obtained were not broken up or analyzed by geographical areas.

Statistical analysis

Independent and dependent variables were described according to their frequency and distribution measurements (arithmetic mean, standard deviation and median). Student's t test, Mann Whitney test, or chi square test were used to compare the distribution of dependent variables among the groups under investigation, depending on the type of variable and its distribution. For bivariate and multivariate models, blood lead and urine parameters were skewed and were natural-log transformed to minimize influential data points, and after to run the statistical models. The data obtained was exponentiated and expressed as arithmetic values for ease interpretation. Linear regression models were used to assess crude or independent associations between study variables with blood lead levels. In the multivariable analysis (generalized estimating equations), we included those statistical significant variables ($p < 0.05$) identified in the bivariate model and those possessing biological plausibility. All analyses were performed with STATA 11.0 software (Stata Corp., College Station, TX, USA).

Results

A total of 480 subjects were included in the study. Demographic characteristics of the study population are presented in table 1. The average age of studied volunteers was 26.5 (range 16-48 years). The ratio women:men was 4:1 and the women average age was significantly higher than in men (27.8 vs 21.0 years) ($p < 0.01$).

The researched population has been followed-up for an average of 11.3 years; seven participants have been followed-up by more than 20 years.

The studied subjects were divided into the three exposure Categories (I-III). Ages, gender, years of residency, anemia, and

Table 2: Biochemical markers of renal function and blood lead levels. Results are shown as arithmetic mean, standard deviation, frequency and percentage [median].

	Category I (< 25 µg/dL) (n = 367)	Category II (≥ 25 - <45 µg/dL) (n = 87)	Category III (≥ 45 µg/dL) (n = 26)
Urea nitrogen serum levels (mg/dL)	21.8 ± 6.8 [21.0]	21.3 ± 6.29 [22.0]	22.1 ± 7.2 [21.5]
Abnormal urea nitrogen level (> 50.0 mg/dL)			
Yes	0	0	0
No	367 100.0%	87 100.0%	26 100.0%
Creatinine serum level (mg/dL)	0.74 ± 0.13 [0.73]	0.74 ± 0.18 [0.70]	0.74 ± 0.1 [0.79]
Abnormal creatinine levels (> 1.20 mg/dL)			
Yes	17 4.6%	8 9.2%	1 3.8%
No	350 95.3%	79 90.8%	25 96.1%
Uric acid serum levels (mg/dL)	4.6 ± 1.19 [4.5]	4.8 ± 1.48 [4.7]	4.9 ± 1.71 [4.35]
Abnormal uric acid levels (> 50.0 mg/dL)			
Yes	13 3.5%	9 10.3%*	3 11.5%*
No	352 96.4%	78 89.6%	23 88.4%
Current proteinuria			
Yes	16 4.3%	2 2.3%	0
No	351 95.6%	85 97.7%	26 100.0%
eGFR (mL/min/1.73m^2)	108.6 ± 28.4 [103.7]	121.0 ± 26.9* [115.8]	121.3 ± 25.2* [115.8]
Zinc protoporphyrin (gr/mL)	3.2 ±2.5 [2.7]	2.5 ± 2.4* [2.1]	2.3 ± 1.6 [1.8]
Baseline BLL (µg/dL)	9.0 ± 6.1 [7.4]	31.7 ± 8.4* [31.6]	54.0 ±12.5* [53.8]
Highest BLL (µg/dL)	10.2 ± 6.1 [8.6]	33.9 ± 7.3* [32.8]	58.8 ± 7.4* [59.6]
Last BLL (µg/dL)	3.0 ± 2.3 [2.5]	4.3 ± 4.2* [3.1]	4.4 ± 2.66* [4.0]
Years of follow-up	11.3 ± 4.3 [11.0]	14.4 ± 2.2* [14.0]	14.3 ± 0.4* [14.0]
Number of blood samples	6.0 ± 4.6 [4.0]	14.5 ± 9.1* [13.0]	28 ±12.2* [25.5]

*$p < 0.05$ Student's t test, or Mann-Whitney test or Chi^2 test (category I vs category II or III)

the frequency of exposure to X-ray and chemical compounds were higher in subjects from Category I ($p < 0.03$). On the other hand, coffee consumption, uric acid, and zinc protoporphyrin levels were higher in Category II ($p < 0.05$), and all the lead´s variables were statistically different between the less exposed subjects (Category I) against the most exposed (II and III) ($p < 0.03$) (Table 1 and Table 2). No statistical differences were found in the rest of the analyzed variables among the studied Categories (Table 1).

The years of follow-up and the number of blood samples taken for lead measurement were higher in Categories II and III ($p < 0.05$), as well as, the average age in the baseline BLL was lower in these two last categories (Table 2).

Less than 10% of the population was exposed, through occupational exposure, to chemical compounds (mainly to volatile organic compounds and welding fume). Participants from Category II had the biggest history of working years (Table 1).

Moderate to severe dehydration (those subjects that necessarily required treatment with salts and fluids intravenously at health institutions) due to diverse etiologies was recorded in < 5% of the population, and the higher frequency of this pathology was recorded in subjects from Category III (Table 1). The frequencies of abnormal urea nitrogen and creatinine serum levels were similar in the three studied Categories. The frequency of abnormal uric acid serum concentration was higher in subjects from Category II and III compared with the frequency registered of this abnormal parameter in Category I ($p < 0.02$) (Table 2); however, when the BLLs were compared in the overall volunteers with abnormal uric acid levels against those with normal uric acid levels (3.3 vs 3.9 µg/dL) no differences were found ($p > 0.05$).

In the urine analysis, proteinuria was detected in only 3.7% of the population and no differences were found in terms of proteinuria frequency among the different categories. Leukocyturia was detected in 20% of urine samples, which 87% of subjects did not refer any clinical urinary symptoms (Table 2). No significant associations were found between proteinuria and any variable analyzed.

The average eGFR in the population was 111.5 ± 25.5 mL/ minute/1.73 m^2. Eighty eight subjects (18.1%) had an eGFR below 90 and only one participant (0.2%),from Category II, had an eGFR below 60. eGFR was significantly lower in participants from Category I when compared with the eGFR values from Categories II and III ($p < 0.02$) (Table 2). No correlation or association was found between eGRF with BLL or with proteinuria.

Zinc protoporphyrine serum levels were significantly lower in Categories II and III when compared with the registered in participants from Category I ($p < 0.05$) (Table 2).

The average number of blood samples for lead measurement was 8.7 (range 2 - 53) and it was higher in Categories II and III ($p < 0.05$) (Table 2).

The mean highest BLL registered in the studied subjects was 17.2 µg/ dL (range 0.2 - 71) (Table 2). The mean BLL registered in the last blood sample from the overall volunteers was 3.3 µg/ dL, and no differences were found between Categories (Table 2).

In the bivariate analysis, abnormal urea nitrogen serum levels were positively associated with creatinine and uric acid levels; meanwhile, the frequency of abnormal creatinine serum levels was positively related with urea nitrogen and uric acid serum levels. Abnormal uric acid levels were positively linked with creatinine levels, BLL baseline sample and with the highest BLL sample. A negative association was found between eGFR with the baseline and the highest BLL (Table 3).

In the multiple linear regression analysis, a positive relation was found between urea nitrogen with creatinine levels. Regarding to the abnormal creatinine levels, the three variables found in the bivariate analysis preserved their significant association, meanwhile, for abnormal uric acid concentration; only years of work remained significantly associated. The relation found for eGFR with the BLL baseline sample and with the highest BLL sample in the bivariate model, did not persist, however, a positive and a negative associations were registered between eGFR with creatinine and with uric acid, respectively (Table 4).

Table 3: Bivariate linear regression models to evaluate associations between biochemical markers of renal function with some demographic variables, with kidney biomarkers and with blood lead levels.

	β	P	95% CI
BUN levels			
Anemia	-2.57	0.006	-4.42 - 0.724
Creatinine levels	13.91	0.000	9.79 - 18.02
Uric acid levels	0.694	0.004	0.225 - 1.164
Abnormal creatinine levels			
Gender	-0.212	0.000	-0.260 - 0.165
BMI	-0.003	0.023	-0.006 - 0.0005
BUN levels	0.005	0.000	0.002 - 0.008
Uric acid levels	0.055	0.000	0.040 - 0.070
Abnormal uric acid levels			
Gender	-0.175	0.000	-0.223 -0.127
Age (years)	-0.002	0.028	-0.005 -0.0002
BMI	0.003	0.018	0.0005 - 0.006
Years of work	0.003	0.049	0.007 - 0.101
Creatinine levels	0.364	0.000	0.226 - 0.502
BLL baseline sample	0.002	0.001	0.0009 - 0.003
Highest BLL	0.002	0.002	0.0007 - 0.003
eGFR			
Baseline BLL	-0.005	0.000	-0.008 -0.003
Highest BLL	-0.005	0.000	-0.007 -0.003

Table 4: Multivariate linear regression models to evaluate associations between biochemical markers of renal function with some demographic variables, with kidney biomarkers and with BLL.

	β	P	95% CI
BUN*			
Creatinine levels	13.13	0.000	8.61 - 17.65
Abnormal creatinine levels**			
Gender	-0.171	0.000	-0.236 - 0.105
BMI	-0.005	0.002	-0.008 - 0.001
BUN	0.003	0.025	0.0004 - 0.007
Uric acid levels	0.051	0.000	0.031 - 0.071
Abnormal uric acid***			
Years of work	0.003	0.017	0.0006 - 0.006
eGFR[&]			
Creatinine	1.33	0.000	1.08 - 1.58
Uric acid	-0.044	0.001	-0.070 - 0.018

*Adjusted for uric acid levels, creatinine levels, anemia, and history of kidney disease.

**Adjusted for gender, age, BMI, BUN, uric acid levels.

***Adjusted for gender, age, BMI, years of work, creatinine, highest BBL, baseline BLL and category II.

[&]Adjusted for age, gender, baseline and highest BLL, proteinuria.

Discussion

Lead is a widespread toxicant with well-established detrimental health effects from which lead nephropathy has been well documented in occupationally exposed workers. However, there is increasing evidence that toxic effects may occur at much lower exposure levels than those observed in occupational settings or in severely polluted environments. In our work, the studied population has been environmental exposed to lead since childhood or/ and adolescence; some of them, for more than 21 year, and few have been followed since their delivery. These facts, importantly strengthens our study because most of the studies reported associating lead exposure and renal function have been carried out in adults (mean age of 50 years and older) who may have a high prevalence of comorbid conditions and kidney disease risk factors, such as diabetes mellitus, hypertension, and smoking [11,12]. Whereas, our work was implemented in children and adolescents who are generally free from these comorbidities. Therefore, and according with the design of our study, the influence of comorbidities on renal function have been reduced significantly, and so, the direct side effects of lead on kidney function could be ascertained. In addition, the statistical analyses were adjusted by the main reported risk factors for declining renal function.

The environmental pollution at which have been exposed our population is reflected in the persistent very high BLL registered in

children and adolescents who live around the fourth biggest smelter in the world [19], from the studied subjects ~ 10 percent had high BLL (> 40 μg/dL).

Acute high-level exposure to lead causes damage to the proximal tubule in the kidney, and chronic lead exposure is an established cause of interstitial fibrosis in the kidney, possibly through lead-induced oxidative stress [1]; whereas, chronic exposure induces proximal tubular atrophy associated with interstitial fibrosis and vascular changes [20-23]. The molecular mechanisms implicated in toxicity from lead or cadmium also share several similarities. Both metals are divalent cations which inhibit sulfhydryl group-containing enzymes [24]. Substantial experimental evidence implicates oxidative stress via oxidation-reduction-inactive metal pathways for both lead and cadmium, resulting in increased reactive oxygen species that lead to depletion of nitric oxide and secondary up-regulation of endothelial nitric oxide synthase [25-29]. Changes in intracellular calcium homeostasis [28,29] and activation of protein kinase C may also be involved [26,28]. Alterations in cell adhesion molecules in renal proximal tubules and endothelium appear to be important mechanisms for cadmium-related nephrotoxicity [29] and may be involved in lead nephrotoxicity as well [30].

When we assessed renal function by the routine biochemical tests such as BUN, creatinine and uric acid concentrations, not differences were found between the studied Categories. However, and according with several studies using creatinine-based estimates of kidney function in healthy populations, our data could underestimate the adverse association of blood lead levels on kidney function because chronic lead nephropathy can be missed in its early stages because of changes induced by chronic low-level lead exposure are subtle and not reflected by changes in routine renal function tests such as BUN and serum creatinine concentrations. Measurement of urinary excretion of urinary biomarkers of kidney tubular dysfunction such as N-acetyl-β-D-glucosaminidase, retinol binding protein, cystatin C level, and α-1-microglobulin will provide most sensitive means to evaluate renal tubular dysfunction after lead exposure.

Hyperuricemia was found in 4.3 % of the studied population. In subjects with uric acid >7 mg/dL, the baseline and highest BLLs were significantly higher ($p < 0.05$) when compared with those with normal values of uric acid, however, this difference was not observed with the value registered in the last BLL. The association between lead exposure and uric acid elevation has been documented in various studies analyzing the association between various lead exposure biomarkers, kidney function index and serum uric acid level in both occupationally exposed [31] and general population [32]. High levels of uric acid are known to be nephrotoxic; however, controversy exists as to whether observed relations between lower levels of uric acid and renal dysfunction are causal or due to misperception. Recently, a rodent model of hyperuricemia was developed [33] and vascular outcomes similar to those noted in humans with primary hypertension [34] and/or renal dysfunction [35], was observed in these rats. In humans, uric acid was found to be associated with reduced renal blood flow and increased renal vascular resistance in patients with primary hypertension [36]. Thus, uric acid may be nephrotoxic at lower levels than previously recognized, as opposed to being simply a marker for other renal risk factors. On the other hand, the frequency of abnormal uric acid serum levels (hyperuricemia) was significantly higher in participant from the most exposed Categories (II, III). In the bivariate statistical analysis, abnormal uric acid frequency was positive associated with the baseline and the highest BLL samples, as well as, with years of work; however, in the multivariate model, only years of work remained positively associated. Most of subjects with hyperuricemia reported occupational contact mainly with organic solvents and secondly with welding fumes. It has been reported that the exposure to those compounds cause occupational renal disorders [37-39] and that some renal function parameters such as GFR decreases with work duration [40]. In addition to occupational exposures, the screening of other co-morbidities or renal disorders risk factors through medical surveillance with periodic examination for screening of non-occupational and occupational disorders, especially risk factors for kidney could be helpful and beneficial.

According with the previously established parameters for renal function, only one subject from category II had an impaired kidney function (serum creatinine > 1.2 mg/dL and eGFR < 60 mL/min/1.73m^2). In this participant, his highest BLL (34.3 μg/dL) was found when he was two years old, and had a history of heavy smoking and alcohol intake; the rest of the study population had a mean creatinine (0.74 ± 0.14 mg/dL) and eGFR (111.5 ± 25.5 mL/min/ 1.73m^2) values within the "acceptable range". eGFR was higher ($p < 0.03$) in the most exposed Categories, however, the 99.8% of the eGFR values found in the three categories are within the "acceptable values". eGFR was associated in the bivariate analysis with the baseline and highest BLL, however, in the multivariate model this association did no remained significant, but a positive association with creatinine and with uric acid were recorded. Lead has been positively associated with eGFR measure and creatinine levels [13,41,42]. Although the mechanisms of lead nephrotoxicity are incompletely characterized, it has been reported that higher blood lead levels increase eGFR by glomerular hyperfiltration which modify serum creatinine levels. In addition to being filtered by the glomerulus, data suggest that creatinine is secreted in the proximal tubule of the kidney via both organic cation and anion transporters [43-45]. Recent data also indicates that heavy metals pass through the basolateral membrane of the renal proximal tubular cells [46] via the same organic cation transporters used for creatinine. According with these results and ours, lead exposure may induces renal proximal tubular cells increasing the GFR (hyper filtration) and modifying negatively the creatinine serum levels.

Previous studies examining the association between lead and kidney function in children and adults with and without kidney disease have reported conflicting associations [47,48]. Chronic nephropathy, subsequent to childhood lead poisoning, has been reported from Queensland, Australia. However, studies from the United States have failed to show any sequel in children up to 35 years after childhood lead poisoning [13]. In other studies, an association between blood lead level and serum cystatin C was observed in Belgian adolescents [13]. In US adolescents, blood lead levels were associated with decreased cystatin C-based eGFR levels [49]; however, the association with creatinine-based eGFR was not statistically significant [50]. In a cross-sectional study of European children, higher blood lead levels were associated with lower serum cystatin C and creatinine levels and these paradoxical associations were attributed to hyperfiltration [12]. Second, reverse causation, specifically increased the blood lead levels as a result of reduced kidney excretion, cannot be excluded due to the cross-sectional study design. These controversial results are probably due to that several studies including our study, the kidney function has been evaluated by means of estimating GFR instead of directly measuring it. It is known that estimated GFR may have greater inaccuracy in general populations compared with CKD patients [51]. Moreover, the MDRD equation was developed in an adult population from the United States [52-54]. Further longitudinal and controlled studies are required with the aim to assess whether if chronic lead exposure contributes to the decrement of kidney function in other different populations and ethnic groups.

Conclusion

Our data suggest that there was no significant association in the multivariate statistical model between BLLs and the eGFR or biochemical markers of renal functions in this cohort of children and adolescents without CKD or without comorbidities.

Acknowledgements

We thank Argelia de la Cruz for the recruitment of participants.

Funding

This work was supported in part by the University of Coahuila (grant number UAdeC-15-0494) and by the National Secretary of Health.

Conflicting of Interests

The author(s) declared no potential conflicts of interests with respect to the research, authorship, and/or publication of this article.

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