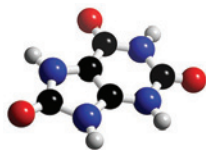


# Association of Lead Exposure, Serum Uric Acid and Parameters of Renal Function in Nigerian Lead-Exposed Workers

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## Abstract

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**Background:** The presence of hyperuricemia and renal function impairment, especially in the absence of urate stone formation is strongly suggestive of lead nephropathy. The evaluation of this association is essential in areas where lead exposure is still prevalent and uncontrolled.

**Objective:** To determine the relationship between serum uric acid and renal function indices in lead-exposed workers.

**Methods:** A cross-sectional study of 190 adults with occupational lead exposure and 80 adults (comparison group), matched for age and sex was performed in Port Harcourt, South-south Nigeria. Blood lead was used as the biomarker of lead exposure while serum urea, serum creatinine, urine albumin (using urine albumin:creatinine ratio), estimated glomerular filtration rate (GFR) and serum uric acid were the renal function indices measured.

**Results:** Occupationally lead-exposed subjects had a significantly ( $p = 0.008$ ) higher mean $\pm$ SD blood lead levels ( $50.37\pm 24.58$   $\mu\text{g/dL}$ ) than the comparison group ( $41.40\pm 26.85$ ). The mean $\pm$ SD serum urea ( $8.6\pm 2.3$   $\text{mg/dL}$ ), creatinine ( $1.0\pm 0.2$   $\text{mg/dL}$ ) and serum uric acid ( $4.6\pm 1.2$   $\text{mg/dL}$ ) were significantly ( $p < 0.01$ ) higher in the study subjects than the comparison group ( $7.6\pm 2.4$ ,  $0.9\pm 0.2$ , and  $3.9\pm 1.1$   $\text{mg/dL}$ , respectively). The mean $\pm$ SD creatinine clearance was significantly ( $p = 0.002$ ) lower in the study subjects than the comparison group ( $98.9\pm 21.3$  vs.  $108.2\pm 25.2$   $\text{mL/min/1.72 m}^2$ ). Serum uric acid level correlated positively with serum creatinine ( $r = 0.134$ ) and negatively with GFR ( $r = -0.151$ ).

**Conclusion:** People with occupational lead exposure are at risk of developing hyperuricemia and renal impairment.

**Keywords:** Lead poisoning; Hyperuricemia; Kidney disease; Kidney failure; Uric acid; Occupational exposure

## Introduction

Lead exposure has been associated with renal function impairment and increased serum uric acid level.<sup>1-5</sup> Hyperuricemia associated with lead toxicity occurs in both acute and chronic lead nephropathy,<sup>6</sup> and is thought to be due to

isolated proximal tubular defects<sup>6-8</sup> resulting in increased tubular reabsorption and reduced secretion of uric acid, as well as lead induced inhibition of guanine aminohydrolase—an enzyme involved in purine metabolism<sup>9</sup>. The resultant hyperuricemia from lead toxicity can then mediate both hypertension and further kidney inju-

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ry.<sup>10,11</sup> It has been shown that elevated uric acid levels can cause endothelial dysfunction through the stimulation of vascular smooth muscle proliferation,<sup>10,11</sup> resulting in thickening of the afferent arterioles of the glomerulus. Hyperuricemia is also known to inhibit the release of nitric oxide within the vasculature of the kidneys, hence reducing renal blood flow and glomerular filtration.<sup>10,11</sup>

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 indices and serum uric acid level in both occupationally-exposed<sup>11-13</sup> and general population<sup>2,14</sup>.

It has also been reported that the increase in serum uric acid level resulting from lead toxicity occurs at much lower lead doses than previously thought.<sup>11,14-16</sup> Similarly, it was also shown that mild elevation of uric acid is associated with subclinical kidney disease in lead-exposed people.<sup>10,11,15</sup>

Nigeria is a country where lead exposure is still prevalent and uncontrolled.<sup>17-19</sup> The objective of this study was to evaluate the association between serum uric acid level and renal function indices among subjects with occupational lead exposure in Port Harcourt, Nigeria.

## Patients and Methods

A cross-sectional study was carried out among adults living in Port Harcourt, Nigeria. The study population was divided into two groups: study subjects with occupational risk for lead exposure, who had been engaged in such occupations for over one year and a comparison group consisted of age- and sex-matched hospital workers with limited occupational risk for lead exposure. The minimum sample size was calculated to be 189 using a prevalence rate of 14.3%—WHO estimated popula-

tion of Nigerian adults with blood lead levels >20 µg/dL.<sup>18</sup> A total of 190 subjects and 80 people (comparison group) using a minimum ratio of three subjects to one comparison who met the inclusion criteria were recruited and participated in the study. Inclusion criteria for the study subjects included residence in Port Harcourt, age between 18 and 60 years and engagement for over one year in any of the following occupations: petrol attendants and petrol refinery workers; battery factory workers and wet cell battery chargers; car radiator repairers; painters and paint pigment workers; and welders and corrosion pipe fitters.

The subjects were selected by random sampling method stratified by occupation, from the following occupational groups: welding/metal work, paint/pigment workers, radiator repairers, battery workers and petrol workers, using a differential sampling ratio range of 0.45 to 0.5 for each occupational subgroup. Subjects in each subgroup were then recruited by consecutive simple random sampling. Non-response was eliminated by continuous recruitment till the sample size limits were achieved.

Subjects with hypertension, diabetes mellitus, evidence of previous renal disease, habitual use of mercury and hydroquinone (nephrotoxicants) containing cosmetics, allopurinol treatment and significant analgesic abuse—defined by a cumulative life time use of over 20 points<sup>20</sup> were excluded from the study.

All study participants signed a written informed consent. The Ethics and Research Committee of the University of Port Harcourt Teaching Hospital approved this study. A clinical evaluation including socio-demographic assessment, and taking clinical and occupational history, were done.

A total of 10 mL blood was collected from each participant for the analysis of

**Table 1:** Demographic characteristics of the study subjects

Parameters	Frequency distribution of variables	n (%)	Range	Mean±SD
Age (yrs)	18–30	78 (41.6)	18–58	34.8±10.1
	31–40	49 (25.8)		
	41–50	42 (22.1)		
	51–60	21 (11.1)		
Sex	Male	151(79.5)		
	Female	39 (20.5)		
Marital status	Married	109(57.4)		
	Single	81 (42.6)		
Occupation	Welding and metal	42 (22.1)		
	Paint and Pigment	38 (20.0)		
	Radiator repairer	37 (19.5)		
	Battery workers	37 (19.5)		
	Petrol	36 (18.5)		
Cigarette smoking (Pack yrs)	Smokers	9 (4.7)	0–15	0.4±2.4
	Non-Smokers	181 (95.3)		
Alcohol consumption (g/wk)	Take alcohol	53 (27.9)	0–216	19.3±4.1
	Do not take alcohol	137 (72.1)		
BMI (kg/m <sup>2</sup> )	<18.5	4 (2.1)	16.9–40.7	24.9±3.6
	18.5–24.9	97 (51.1)		
	25–29.9	74 (38.9)		
	30–34.9	13 (6.8)		
	35–39.9	1 (0.5)		
	>40	1 (0.5)		

biochemical and hematological parameters. The laboratory assessment of renal function and other parameters was done at the University of Port Harcourt Teaching Hospital clinical chemistry and hematology laboratories. The venous blood lead level was measured in subjects as a marker of lead exposure. Venous blood sample was collected in sealed plastic containers with no anticoagulant, and analyzed by atomic absorption spectrometry. Serum urea, serum creatinine and uric acid were assessed using venous blood collected in lithium heparin and EDTA. Creatinine clearance was calculated using the Cockcroft and Gault formula:<sup>21</sup>

$$\text{Creatinine Clearance}_{\text{(mL/min)}} = \frac{(140 - \text{Age}_{\text{(yr)}}) \times \text{Body Weight}_{\text{(kg)}} (\times 0.85 \text{ for women})}{\text{Plasma Creatinine}_{\text{(mg/dL)}} \times 72}$$

The estimation of urine albumin was done using the urine albumin:creatinine ratio (ACR) after the collection of spot urine samples.

Data were analyzed by SPSS® ver 14 for Windows®. The results of continuous parameters are presented as Mean±SD. *Student's t* test for independent samples, and one-way analysis of variance (ANOVA) were used to compare means of two and more groups. Categorical variables were compared using  $\chi^2$  test. Pearson's bivariate correlation coefficient and linear regression analysis were used to assess the level of relationship between blood lead and uric acid levels, renal function indices and other study variables. A p value <0.05 was considered statistically significant.

**Table 2:** Demographic characteristics of the comparison group

Parameters	Frequency distribution of variables	n (%)	Range	Mean±SD
Age (yrs)	18–30	26 (33)	19–59	36.0±10.1
	31–40	24 (30)		
	41–50	19 (24)		
	51–60	11 (14)		
Sex	Male	58 (73)		
	Female	22 (28)		
Marital status	Married	25 (32)		
	Single	55 (69)		
Occupation	Hospital workers	80 (100)		
Cigarette smoking (Pack yrs)	Smokers	3 (4)	0–10	0.3±1.6
	Non-Smokers	77 (96)		
Alcohol consumption (g/wk)	Take Alcohol	20 (20)	0–126	12.2±26.7
	Do not take alcohol	60 (75)		
BMI (kg/m <sup>2</sup> )	<18.5	1 (1)	18.3–48.0	26.1±5.1
	18.5–24.9	39 (49)		
	25–29.9	24 (30)		
	30–34.9	13 (16)		
	35–39.9	2 (3)		
	>40	1 (1)		

## Results

Demographic characteristics of the study population are presented in Tables 1 and 2. The mean±SD age of lead-exposed subjects (34.8±10.1 yrs) was not significantly ( $p = 0.385$ ) different from that of the comparison group (36.0±10.1 yrs) (Table 3). Although there was a higher proportion of male participants, no significant ( $p = 0.21$ ) difference was observed in the male:female ratio in the two studied groups (Tables 1 and 2).

The mean±SD duration of occupation in the study subjects was 11.9±9.3 (range: 2–48) years, while in the comparison group, it was 8.0±7.3 (range: 2–30) years ( $p = 0.001$ ) (Table 3).

The mean±SD blood lead level in subjects (50.4±24.6 µg/dL) was significantly ( $p = 0.008$ ) higher than that of the comparison group (41.4±26.9) (Table 3).

The measured renal function indices of the studied groups are shown in Table 3. The mean calculated creatinine clearance was significantly ( $p = 0.002$ ) lower in the study subjects compared with the comparison group (Table 3). The mean urinary albumin excretion was not statistically different between the two studied groups ( $p = 0.316$ ) (Table 3).

Serum uric acid level correlated positively with serum creatinine level ( $r = 0.134$ ,  $p = 0.028$ ) and negatively with creatinine clearance ( $r = -0.151$ ,  $p = 0.013$ ) (Figs 1 and 2). In multiple regression anal-

**Table 3:** Comparison of study variables between the study subjects and the comparison group

Variables	Study subjects(n=190) Mean±SD	Comparison group (n=80) Mean±SD	p value
Age (yrs)	34.8±10.0	36.0±10.1	0.385
Duration of occupation (yrs)	11.9±9.3	8.0±7.3	0.001
Alcohol use (g/wk)	19.3±41.1	12.2±26.8	0.152
Cigarettes (pack yrs)	0.5±2.4	0.3±1.6	0.555
BMI (kg/m <sup>2</sup> )	24.9±3.6	26.1±5.1	0.028
Blood lead level (µg/dL)	50.4±24.6	41.40±26.9	0.008
Fasting blood sugar (mg/dL)	75.9±10.6	74.2±9.6	0.240
Urea (mg/dL)	8.6±2.3	7.6±2.4	0.002
Creatinine (mg/dL)	1.0±0.2	0.9±0.2	0.001
Uric acid (mg/dL)	4.6±1.2	3.9±1.1	0.000
Creatinine clearance(mL/ min/1.73 m <sup>2</sup> BSA)	98.9±21.3	108.2±25.2	0.002
Urine Alb (mg/g Cr)	31.0±13.3	32.7±11.7	0.316

ysis, the association between serum uric acid level and creatinine clearance still remained significant and was only modified by age after adjustment. In other models adjusted for gender, blood lead level and smoking status, and urine albumin excretion, no significant effect modification was observed.

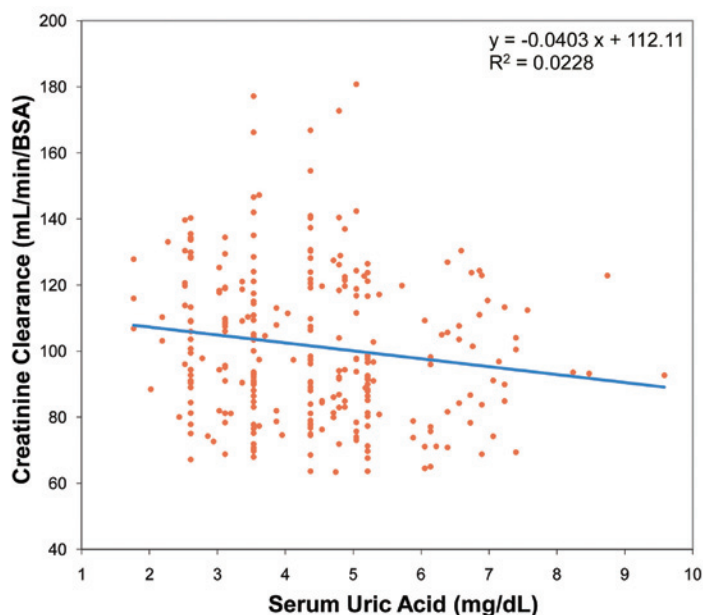
Blood lead level was not associated with uric acid neither in single linear model nor after adjusting for other study variables. It, however, correlated positively with blood urea level ( $r = 0.031$ ).

### Discussion

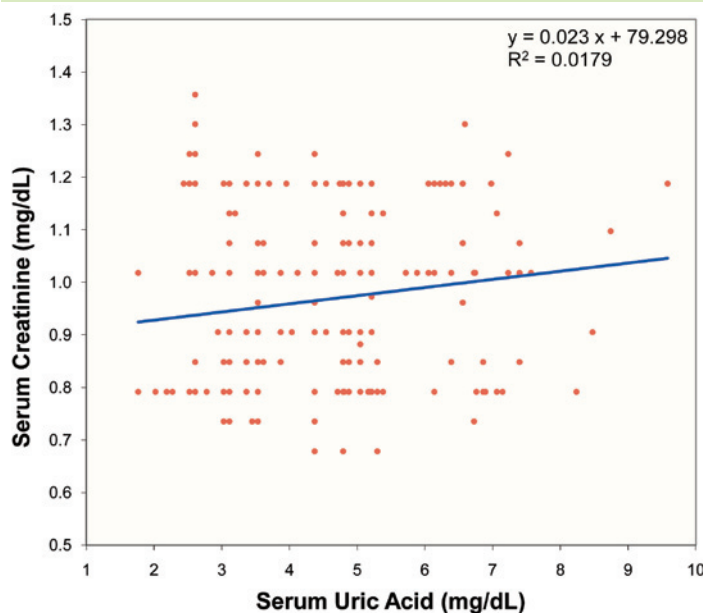
The association between occupational lead exposure, gout and renal function impairment is well-known.<sup>2,4,14,22</sup> This study done in a population with relative lead over-exposure,<sup>17-19</sup> sought to evaluate the

degree of occupational lead exposure and the relationship between serum uric acid level and renal function indices in lead-exposed workers. The results of this study established significantly higher mean blood lead in the study subjects compared to that in the comparison group. This finding is consistent with reports from other Nigerian studies by Anetor<sup>23</sup> who reported a mean±SD blood lead concentration of 56.3±1.0 µg/dL in occupationally exposed subjects compared to 30.5±1.4 µg/dL in controls, and Ogunshola, *et al*,<sup>24</sup> who reported a higher mean±SD blood lead level of 18.1±6.4 µg/dL in traffic wardens compared to 12.9±7.0 µg/dL in controls in Lagos. This trend has also been established by reports of studies in other countries. A study of Korean lead workers reported a mean±SD blood lead level of 32.0±15.0 µg/dL compared with 5.8±1.8 µg/dL in

controls.<sup>11</sup> Similarly, Jung, *et al*,<sup>25</sup> reported the following mean±SD blood lead levels of 74.6±7.8, 46.5±5.9 and 24.3±2.7 µg/dL, respectively, in the highly-, moderately- and slightly-exposed lead workers and 7.9±1.4 µg/dL in the control group. Pergande and coworkers in a German study<sup>26</sup> also reported higher mean blood lead level of 40.6 (range: 20.2–70.6) µg/dL in lead workers against 6.8 (range: 4.8–10.6) µg/dL in the controls. Medhi, *et al*,<sup>27</sup> from Iraq also reported higher mean blood lead concentrations of 71.7, 58.0 and 36.4 µg/dL in three groups of lead exposed workers compared with 14.6 µg/dL in controls. The results from this study, therefore, signify a higher degree of lead exposure in occupational exposed persons in Port Harcourt in comparison with the comparison group, with an extrapolated higher risk of adverse health effects due to lead toxicity such as renal impairment in the study population. The similarity in the value of the mean±SD blood lead levels of 50.3±24.5 µg/dL reported in our study and the value of 50.6 reported by Anetor<sup>23</sup> in Ibadan, South West Nigeria, may reflect a kind of uniformity in the National occupational lead exposure risk, especially with similarities in the occupational groups studied. The variance in the mean±SD blood lead of 18.1±6.4 µg/dL reported by Ogunshola, *et al*,<sup>24</sup> in a study on traffic wardens in Lagos, may be explained by the difference in the occupational groups studied. Furthermore, the difference may be attributed to time trends in the degree of lead exposure from 1994, when the report by Ogunshola was published, and 2002 when report of Anetor was published and 2008 when our study was carried out. The significance of the findings of our study is underlined by the guidelines of the Occupational Safety and Health Administration (OSHA) Lead Standard<sup>28</sup> which recommend that medical evaluation must be performed on workers with blood lead levels ≥40 µg/dL. The



**Figure 1:** Scatter plot of serum uric acid vs creatinine clearance



**Figure 2:** Scatter plot of serum uric acid vs creatinine level

significant degree of occupational lead exposure reported in our study may further be explained by the poor regulation of occupational lead exposure in Nigeria and many of other developing countries,<sup>29</sup> as well as the low level of awareness of lead

**TAKE-HOME MESSAGE**

- Hyperuricemia associated with lead toxicity occurs in both acute and chronic lead nephropathy.
- Hyperuricemia from lead toxicity can mediate hypertension and further kidney injury.
- Increase in serum uric acid level resulting from lead toxicity occurs at much lower lead doses than previously thought.
- Serum uric acid is a significant indicator and predictor of renal impairment in lead-exposed workers.
- Routine screening of occupational lead exposure risk groups for any increase in serum uric acid or decrease in eGFR should be undertaken as part of measures to control and prevent lead-induced chronic kidney disease.

toxicity among people engaged in occupations which put them at risk.

The results of the current study suggest a higher possibility of renal impairment in lead-exposed workers and a significant association and role for uric acid in early development of renal function impairment among the lead-exposed subjects. This assertion is supported by the significantly higher level of serum uric acid, serum urea and serum creatinine levels found in lead-exposed workers compared to those in the comparison group, and the lower values of creatinine clearance in the lead-exposed subjects. Moreover, there were significant positive correlations between blood lead and serum urea levels; significant positive correlation was also observed between serum uric acid and creatinine levels and negative correlation was found between serum uric acid and creatinine

clearance. Similar findings have been previously documented. Pinto de Almeida, *et al*,<sup>30</sup> Weaver, *et al*,<sup>11</sup> and Ahmed, *et al*,<sup>29</sup> reported higher serum uric acid level in lead-exposed workers compared to controls; Wang, *et al*,<sup>13</sup> Jung, *et al*,<sup>25</sup> and Endo, *et al*,<sup>31</sup> also found significantly higher mean serum urea levels in occupationally-exposed subjects compared to controls. The higher mean serum creatinine level observed in this study was also previously reported by Erhlich, *et al*,<sup>12</sup> in South African lead-exposed workers. Similarly, Pergande, *et al*,<sup>26</sup> reported that creatinine clearance was significantly lower in lead-exposed workers compared to controls.

The association between serum uric acid level and creatinine clearance observed in this study was independent of the age-related decline in creatinine clearance. Jung, *et al*,<sup>25</sup> found a significant positive correlation between serum uric acid, serum creatinine and serum urea levels in a study of lead-exposed Korean workers. Higher uric acid was associated with worse renal function as reported by Weaver, *et al*,<sup>11</sup> with a significant positive correlation between serum uric acid, serum creatinine and serum urea levels and a negative correlation with measured and calculated creatinine clearance. In spite of the significant association between serum uric acid concentration and indices of renal function in this study—serum creatinine level and creatinine clearance—there was no correlation between blood lead—a marker for lead exposure—and serum uric acid level, which is in keeping with observations made by Jung, *et al*,<sup>25</sup> and Omae, *et al*.<sup>32</sup> Jung, *et al*,<sup>25</sup> Hsiao, *et al*,<sup>33</sup> and Gerhadsson, *et al*,<sup>34</sup> did not report any significant correlations between blood lead level and serum creatinine. Omae, *et al*,<sup>32</sup> did also not find any association between blood lead level and creatinine clearance. Serum urea was the only index of renal function with significant positive correla-

tion with blood lead level in this study as earlier reported by Jung, *et al*,<sup>25</sup> and Endo, *et al*.<sup>31</sup>

The results of this study revealed a relationship between serum uric acid level and impaired renal function even at relatively normal levels of uric acid. These observations have been previously documented in studies of lead exposed subjects<sup>11,25,31</sup> and apparently healthy cohorts,<sup>35</sup> with the supposition that the relationship between serum uric acid level and renal function indices, like serum creatinine, may be useful in the early detection of renal impairment. The strength of this association is expected to be more significant in lead-exposed subjects as hyperuricemia is an established consequence and promoter of lead nephropathy.<sup>1,6,15</sup> Despite lack of association between blood lead level and serum uric acid level in this study, the results do suggest a role for uric acid in development of renal impairment. The evidence for this is the fact that elevated levels of uric acid independently increase the risk for new-onset kidney disease with significant correlations between serum uric acid level and electronic GFR (eGFR), as shown by Obermayr, *et al*.<sup>36</sup> Furthermore, suggestions that the associations of serum uric acid level and adverse renal outcomes may result in reduced significance of lead biomarker associations,<sup>11,14</sup> may partly explain the findings of our study. In addition, the mean blood lead level of 50.3 µg/dL reported in the study subjects is consistent with reports of an earlier study<sup>11</sup> evaluating the association among blood lead level, serum uric acid concentration and renal function indices, which stated that in apparently healthy subjects, a blood lead level >50 µg/dL is required to establish associations with serum uric acid level and renal function.<sup>12,13</sup>

In conclusion, serum uric acid is a significant indicator and predictor of renal impairment in lead-exposed workers. Fur-

thermore, the risk of uric acid-associated renal impairment in occupational and environmental lead-exposed people may occur at relatively normal levels of serum uric acid. In view of the higher risk of lead exposure in developing countries and the poor regulation of occupational lead exposure among risk groups in Nigeria, it is recommended that the routine screening of occupational lead exposure risk groups for any increase in serum uric acid or decrease in eGFR be undertaken as part of measures to control and prevent lead-induced chronic kidney disease.

**Conflicts of Interest:** None declared.

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