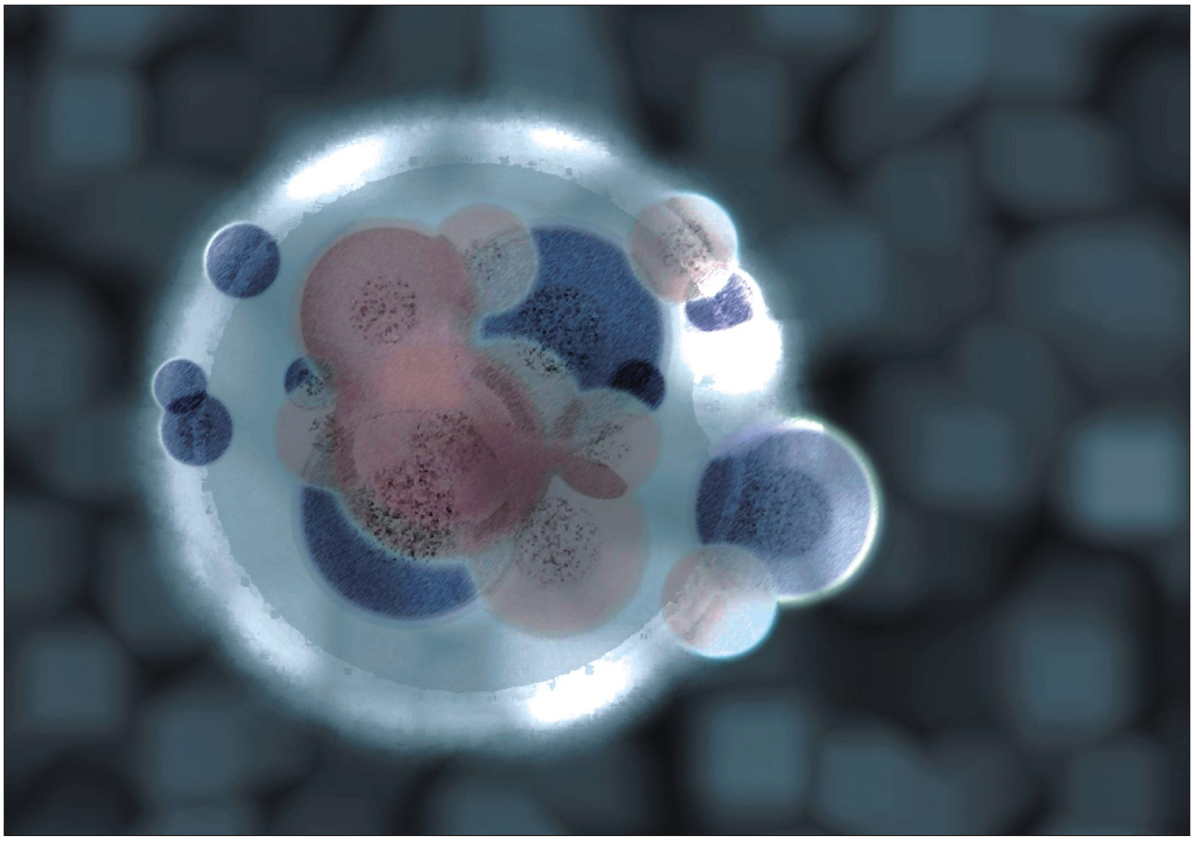

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Research Article
Nephrotoxicity Effect in Inhabitants of a Lead-zinc Mining Community, Ebonyi State, Nigeria

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Abstract

Background and Objectives: The problems posed by mining activities, especially those of heavy metals, to the inhabitants of host communities cannot be overemphasized. This cross-sectional study was undertaken to assess nephrotoxicity of some heavy metals in inhabitants of a lead-zinc mining community in Ebonyi State of Nigeria. **Materials and Methods:** Subjects, aged 10-60 years, included 89 artisanal miners (occupationally-exposed), 61 non-miners living in the same community (environmentally-exposed) and 65 non-miners from a distant community (controls). The heavy metals were estimated using atomic absorption spectrophotometric methods, electrolytes were estimated using ion selective electrodes while urea and creatinine concentrations were determined using enzyme methods. **Results:** Results showed that the mean level of these heavy metals from occupationally-exposed group were significantly higher than their levels in both environmentally-exposed and control groups, irrespective of their gender. Also, the mean levels of the metals from environmentally-exposed group were significantly higher than those from the control group. Furthermore, there were significant differences in the kidney function parameters between the occupationally-exposed group and the environmentally-exposed and control groups on one hand and between environmentally-exposed group and control group on the other hand. **Conclusion:** The results indicate that these metals have nephrotoxic effects on both occupationally-exposed and environmentally-exposed subjects in the community. Therefore, this study advocates for routine monitor of exposed inhabitants of all mining communities to detect early kidney toxicity in order to institute adequate actions to ameliorate it.

Key words: Nephrotoxicity, heavy metals, mining communities, exposed

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Epidemiological studies have shown that environmental toxicants are known to play significant roles in the development of chronic renal diseases[1,2]. The most prevalent environmental toxicants of much interest in the development of kidney disease include cadmium, lead, arsenic and mercury[3]. They are usually disposed as industrial wastes or products of mining activities and are known to be non-biodegradable with long biological half-life, making them to accumulate over time. This long term accumulation makes the onset of the resulting disease almost asymptomatic until the full blown condition appears, thus the prevailing body burden of these toxins at any time is made up of past exposures and current exposure. Another major factor that contributes to the absorption of these toxins is decreased intake of divalent antioxidants like iron and zinc. This is because an iron transporter-divalent metal transporter 1 (DMT-1), located in the duodenum, erythrocytes, liver and cells and known to have high affinity for other divalent metals like cadmium, lead, arsenic etc. are greatly expressed under this condition[4,5]. This expression advantageously increases intestinal absorption of these heavy metals and therefore, their toxicities.

Cadmium (Cd), which is one of the most toxic elements to which humans are exposed, gradually accumulates in the body and levels increase with age given its long half-life[1]. Free Cd accumulates in the mitochondria, blocking the respiratory chain and results in mitochondrial dysfunction and formation of free radicals that activate caspase enzymes and apoptosis process. Offspring of rats exposed to Cd during gestation was found to have decreased renal function, proximal tubular damage and abnormal paracellular tight junctions in the glomeruli in adulthood[6]. Exposure to organic or inorganic lead (Pb) can result in acute or chronic poisoning,[7] making the metal a relevant worldwide health problem. Exposure to high concentrations of Pb has been considered a risk factor for developing high blood pressure and kidney disease. Some studies[8,9] recognized that even what may be termed the blood threshold of Pb (10 μg dL^{-1}) appears to be no more a threshold for safety as this value still has direct effect on kidney function and increases risk of cardiovascular disease. Though occupational controls and removal of lead from paint, gasoline and other environmental sources in developed countries have reduced lead toxicity in these countries[10], such control has not been successful in developing countries due mainly to negligence and poor regulations. Arsenic (As) is one of the most widespread environmental pollutants especially in drinking water[1]. Less common form of exposure is through medications containing As, such as arsenic trioxide used in the treatment of acute promyelocytic leukaemia and other drugs used to treat sleeping sickness and leishmaniasis[11]. Arsenic is absorbed by the intestine, lungs and to a lesser extent skin. There is dearth of information on the clinical manifestation of As toxicity in the kidney but it is expected to manifest as indicators of tubular damage such as low molecular weight proteinuria, aminoaciduria, glycosuria and phosphaturia as well as progressive deterioration of renal function[12]. Mercury (Hg) is a toxic metal found in many environmental and industrial settings in metallic, inorganic and organic forms. Of these, the most encountered environmentally is the organic methylmercury which is formed predominantly when organic mercuric ions are methylated by microorganisms in the soil and water[3]. Exposure to mercuric compounds can be occupational, environmental or dietary[13-15] and they readily accumulate in the kidney, the primary site of accumulation and intoxication[3]. Exposure to all forms of mercury can have nephrotoxic effects[16-18], however, exposure to conjugates of Hg^{2+} leads to the most severe nephropathy[3]. Though kidney disease is often cited as one of the adverse effects of chromium (Cr), much has not been reported about chronic renal disease due to occupational or environmental exposure to it[19]. Kidney is the principal route of elimination of chromium where it is selectively accumulated in the proximal convoluted tubule (PCT)[20]. Therefore, it is expected that kidney disease will result only after long term low dose of the metal, with findings like low molecular weight proteinuria, beta-2 micro-globinuria and retinol-binding proteinuria. However, other studies[21,22] have shown that a low molecular weight protein-chromodulin, which binds and transports chromium, is even helpful in the control of hyperglycemia by amplifying insulin signaling. This ameliorates oxidative stress-an important factor involved in the manifestation of complications of hyperglycemia, including nephropathy.

Considering the adverse effects of these heavy metals, one will be right to suspect that both the miners and inhabitants of a community where these metals are mined will be at risk of organ pathology, including kidney disease-nephrotoxicity[23]. There is dearth of information on the renal integrity of occupationally and environmentally exposed inhabitants of Enyigba lead-zinc mining community of Ebonyi State of Nigeria. Study had reported the risk of continuous use of some plants in this community for purposes of herbal treatment, seeing it as counterproductive because of possible increase of heavy metals in these plants.

MATERIALS AND METHODS

Ethical clearance: Ethical clearance for this study was sought and obtained from Health Research Ethics Committee of College of Medicine, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Nigeria. Further ethical clearance was sought and obtained from the State Ministry of Health, Abakaliki, Ebonyi State while the subjects gave their informed consent after thorough explanation of the importance and procedures for the research.

Study area: This study was carried out between April, 2018 and September, 2019 in a highly mineralized Enyigba community in Abakaliki mining area of Ebonyi State in southeastern part of Nigeria. Abakaliki mining area lies between latitude 6°8'N and 6°24' and longitudes 8°05'S. The prevailing climate conditions are high precipitation that exceeds evapotranspiration rates, high temperatures and humidity for more than half the year. Vegetation types are mangrove and freshwater swamp communities, rainforest, forest/savannah mosaic and derived savannah zones. The inhabitants are mainly subsistent farmers with major crops as yam and plantain, with oil palm bush and indigenous trees of nutritional, economic, medicinal and cultural importance. The Abakaliki lead-zinc is believed to be of hydrothermal origins emplaced at a temperature[24] of about 140°C. The region includes Abakaliki town (the capital city of Ebonyi State) and the highly mineralized rural community (Enyigba) which is about 14 km South of the metropolis. In this study, Enyigba community was purposively selected because it is the largest and most active among mining sites in Abakaliki area. Ezzamgbo, which is about 25 km from the study area with no history of mining activities, was used as a control community.

Subjects: A total of 215 subjects were recruited for the study, comprising 89 (50 males and 39 females) mine workers (occupationally-exposed subjects), 61 (25 males and 38 females) non-workers but living in the community (environmentally-exposed subjects) and 65 (35 males and 30 females) controls who live far (25 km) from the mining community. These subjects were aged between 10 and 60 years.

Laboratory analyses: A total of 6.0 mL of venous blood was collected from each subject. The 4.0 mL was dispensed into sequestrene container for heavy metal analysis while the remaining was put into a chemically clean glass test tube and allowed to clot and retract for kidney function parameters. Separated plasma and sera were stored frozen till day of analysis, which was usually <2 weeks from the day of collection. All analyses were done in duplicates and the average values calculated and used. Plasma heavy metals were estimated by flame atomic absorption spectrometry according to American Public Health Association[25] using FS240AA Atomic absorption spectrophotometer (Agilent Technologies, USA). Serum electrolytes were determined by ion selective electrode method using ISE-SFRI-4000 (Sari Berganton, France). Serum creatinine was estimated by Jaffe reaction as previously described[26] and urea by urease Bertholet method as previously described,[27] using reagents prepared by Roche Diagnostic Ltd on COBAS c111 automated chemistry analyzer (Roche Diagnostic Ltd., Switzerland). Instructions in the product manual were strictly adhered to, to insure reproducibility of the results.

Statistical analyses: Generated data were analyzed using statistical package for social sciences (SPSS). Statistical significance was taken to be $p<0.05$ in all the analysis.

RESULTS

Table 1 shows the mean (±SD) concentrations of the studied heavy metals in the different groups-occupationally-exposed, environmentally-exposed and control groups. The mean value from the occupationally-exposed group was significantly higher than those from environmentally-exposed and control groups. Also, the mean value from environmentally-exposed group was significantly higher than that from control group. Table 2 shows the mean (±SD) values of kidney function parameters of the study population. The mean creatinine, sodium, potassium and chloride values from occupationally-exposed group were significantly higher ($p<0.01$) than those from the environmentally-exposed and control groups while their mean urea and calcium levels were significantly

Table 1: Mean (±SD) values of heavy metals in different study groups

Heavy metals	Controls (n = 65)	Environmentally exposed (n = 61)	Occupationally exposed (n = 80)	p-value
Pb (μg dL^{-1})	4.76 (2.16)	28.66 (9.12)	42.30 (10.90)	<0.001
Hg (μg L^{-1})	3.44 (2.58)	9.31 (8.65)	10.00 (7.26)	<0.001
Cd (μg L^{-1})	2.86 (1.52)	7.31 (6.38)	8.80 (7.56)	<0.001
Cr (μg mL^{-1})	0.04 (0.04)	0.07 (0.12)	0.15 (0.25)	<0.01
As (ng mL^{-1})	4.44 (3.33)	9.55 (7.19)	15.00 (7.19)	<0.001

±SD in parenthesis

Table 2: Mean (±SD) values of kidney function parameters in different study groups

Parameters	Occupationally exposed n = 89 Mean (SD)	Environmentally exposed n = 61 Mean (SD)	Control n = 65 Mean (SD)
Creatinine (μmol L^{-1})	78.24 (34.20)**	75.12 (25.96)**	66.21 (8.40)
Urea (mmol L^{-1})	2.22 (0.96)**	2.20 (1.01)**	2.95 (0.90)
Sodium (mmol L^{-1})	139.37 (18.30)**	139.29 (12.55)**	131.55 (4.63)
Potassium (mmol L^{-1})	4.86 (0.86)**	4.20 (0.62)**	3.78 (0.40)
Chloride (mmol L^{-1})	98.52 (12.52)*	97.34 (8.51)*	91.25 (15.78)
Bicarbonate (mmol L^{-1})	21.47 (2.02)[a]	22.25 (2.11)**	21.13 (1.13)
Calcium (mmol L^{-1})	1.93 (0.24)**	2.11 (0.44)*	2.22 (0.33)

With controls: *p<0.01, **p<0.001, Occupationally vs. Environmentally, [a]p<0.05

Table 3: Mean (±SD) of kidney function parameters of the study population according to age groups

Parameters	Groups	10-20 years	21-30 years	31-40 years	41-50 years	51-60 years	F/p-value
Creatinine	Occupation	66.8 (15.0)	80.4 (20.5)	89.5 (30.9)	77.0 (44.2)	75.5 (16.7)	4.83 (0.001)
	Environment	58.3 (7.8)	77.5 (15.1)	81.1 (20.1)	76.6 (15.8)	99.8 (38.3)	3.79 (0.003)
	Controls	45.2 (5.5)	65.5 (9.4)	70.9 (5.6)	68.3 (4.0)	65.9 (10.8)	2.89 (0.015)
Urea	Occupation	2.00 (0.68)	2.10 (0.58)	2.56 (1.39)	2.72 (1.51)	2.32 (0.82)	1.32 (0.26)
	Environment	1.56 (0.89)	2.75 (1.56)	2.13 (0.64)	2.22 (1.24)	2.52 (1.21)	0.54 (0.78)
	Control	2.68 (0.62)	2.83 (0.79)	3.30 (1.12)	3.01 (0.94)	3.90 (0.99)	1.51 (0.19)
Sodium	Occupation	141.8 (28.0)	137.0 (12.1)	140.7 (19.1)	143.8 (2.7)	137.9 (11.6)	0.36 (0.87)
	Environment	124.0 (13.1)	135.3 (2.8)	142.3 (10.8)	145.7 (16.0)	137.3 (6.1)	2.45 (0.03)
	Control	134.0 (4.9)	131.6 (3.6)	131.6 (4.4)	132.0 (8.0)	130.0 (0.0)	0.96 (0.45)
Potassium	Occupation	4.36 (0.62)	4.05 (0.56)	4.27 (0.77)	4.44 (0.34)	3.95 (0.59)	1.15 (0.34)
	Environment	3.60 (0.26)	4.30 (0.45)	4.25 (0.73)	6.45 (8.88)	4.20 (0.60)	0.45 (0.84)
	Control	3.83 (0.36)	3.88 (0.48)	3.78 (0.35)	3.88 (0.25)	3.40 (0.00)	1.05 (0.40)
Chloride	Occupation	100.6 (18.4)	95.8 (9.9)	99.8 (11,9)	100.4 (6.9)	97.5 (9.4)	0.43 (0.83)
	Environment	88.7 (8.7)	97.7 (2.6)	97.1 (8.4)	101.2 (10.7)	98.1 (6.0)	1.33 (0.26)
	Control	93.7 (6.3)	86.4 (25.7)	93.9 (4.6)	96.4 (5.0)	96.5 (6.4)	0.71 (0.64)
Bicarbonate	Occupation	21.46 (2.32)	20.65 (1.78)	21.46 (1.79)	23.20 (1.92)	23.50 (1.3)	3.76 (0.004)
	Environment	19.33 (4.72)	21.00 (2.00)	22.91 (1.78)	22.83 (1.68)	22.45 (2.1)	1.97 (0.08)
	Control	21.67 (1.11)	21.13 (0.99)	21.11 (0.99)	21.42 (1.71)	20.50 (0.7)	1.42 (0.22)
Calcium	Occupation	1.96 (0.42)	2.13 (0.54)	2.20 (0.43)	2.24 (0.41)	2.01 (0.24)	0.84 (0.51)
	Environment	1.83 (0.55)	2.17 (0.17)	2.27 (0.34)	2.31 (0.33)	2.22 (0.10)	1.54 (0.18)
	Control	2.02 (0.16)	1.91 (0.25)	1.91 (0.26)	2.11 (0.29)	1.60 (0.14)	1.59 (0.16)

±SD in parenthesis

Table 4: Kidney function parameters of the study population according to gender

	Occupationally exposed n = 89		Environmentally exposed n = 61		Control n = 65	
Parameters	Male n = 50	Female n = 39	Male n = 23	Female n = 38	Male n = 35	Female n = 30
Creatinine	86.79 (46.34)*	72.03 (22.37)	83.10 (30.11)*	65.35 (14.03)*	70.18 (5.83)	62.31 (8.76)
Urea	2.28 (0.76)***	2.16 (1.18)*	2.19 (0.95)**	2.32 (1.07)*	3.12 (1.03)	2.78 (0.74)
Sodium	138.64 (7.21)*	140.32 (26.95)	138.54 (9.59)**	139.79 (14.06)**	132.03 (4.38	131.23 (4.91
Potassium	4.73 (0.74)**	4.28 (0.58)**	4.18 (0.48)	4.21 (0.77)***	3.833 (0.38)	3.75 (0.42)
Chloride	97.12 (6.37)*	100.32 (17.70)*	96.83 (7.25)	97.73 (9.20)*	94.40 (5.16)	88.11 (21.93)
Bicarbonate	21.52 (2.00)	21.39 (2.11)	22.41 (1.52)**	22.13 (2.40)*	21.31 (1.14)	20.97 (1.11)
Calcium	1.91 (0.24)***	1.94 (0.25)**	2.11 (0.46)*	2.09 (0.42)**	2.17 (0.24)	2.22 (0.37)

With corresponding controls: *p<0.05, **p<0.001, ***p<0.001

lower (p<0.001) than those from the other groups. At the same time, the values of the same parameters obtained from the environmentally-exposed individuals were significantly higher (p<0.01) than those from the controls, while their urea and calcium levels were significantly lower (p<0.01) than those from the controls. Table 3 presents mean (±SD) values of kidney function parameters across age groups of the study population. The results indicate that only creatinine has positive correlation with the ages of all the groups (F = 4.83, p = 0.001, F = 3.79, p = 0.003, F = 2.89, p = 0.01 for occupationally-exposed, environmentally-exposed and controls respectively), while bicarbonate level has positive correlation with age in occupationally-exposed subjects only (F = 3.76, p = 0.004) and sodium shows positive correlation with age in environmentally-exposed subjects only (F = 2.45, p = 0.03). Table 4 shows the mean (±SD) values of kidney function parameters of the study population according to gender. The mean creatinine, sodium, potassium chloride and bicarbonate levels of the occupationally-exposed males were significantly higher (p<0.05), while the mean urea level was significantly lower (p<0.001) than those obtained from male controls. In females, the mean urea and calcium levels of

the occupationally-exposed were significantly lower ($p<0.05$), while the mean potassium and chloride levels were significantly higher ($p<0.05$) than those from the female controls. Furthermore, in the environmentally-exposed, the mean creatinine, sodium and bicarbonate levels from males were significantly higher ($p<0.05$), while mean urea and calcium levels were significantly lower ($p<0.05$) than those obtained from the male controls. In females, the mean creatinine, sodium, potassium, chloride and bicarbonate levels were significantly higher ($p<0.05$), while the mean urea and calcium levels were significantly lower ($p<0.05$) than those from the female controls.

DISCUSSION

The results from this study showed that both occupationally-exposed and environmentally-exposed groups have significantly higher blood concentrations of the studied heavy metals than the control group. Also, the values from the occupationally-exposed were significantly higher than the values from environmentally-exposed. These portend predisposing factor for organ toxicity among the inhabitants of this community, both miners and non-miners. Though it has been noted that some of these metals still have adverse effects even at tolerable values[8], the values obtained from the control group were quite lower than the tolerable levels, for instance that of lead (10 μg mL^{-1}). Furthermore, the results showed that kidney assessment parameters from occupationally-exposed group were significantly increased when compared with environmentally-exposed and control groups. This significant increase is an indication that these mine workers are predisposed to impaired kidney function. Although, the levels of urea and creatinine from this study appear to fall within the reference intervals for the black population[28,29] for all the studied subjects, the significant increases in their levels between the different groups of the studied subjects justifies the fear of kidney impairment. These findings are in agreement with some recent studies[16,30-35], which had reported chronic nephropathy as irreversible kidney disease that followed months or years of intense exposure to lead and other heavy metals. However, the findings disagree with some other studies[36,37] which reported no renal effects or only intra-clinical changes of marginal significance in workers with low level exposure to lead. Heavy metals are generally toxic at very low doses, non-biodegradable with long biological half-life and are easily accumulated by the kidney where they cause different severity of nephropathy[38,39], in addition to hypertension, neurodegenerative diseases, cognitive impairment and behavioral and psychiatric problems[37,40]. Lead nephropathy, like nephropathy due to other heavy metals, is an irreversible kidney disease that develops over months or years of excessive exposure, thus linking chronic occupational exposure to lead to high incidence of renal dysfunction[30,32]. Moreover, levels of the studied heavy metals from one group were significantly higher than those from subsequent group, it implies that the differences in these kidney assessment parameters were as a result of the differing concentrations of the heavy metals in the different groups. At the same time, the serum calcium levels were significantly lower in occupationally-exposed subjects when compared with those from environmentally-exposed and control subjects. This further supports the possibility of impaired kidney functions, given that both chronic kidney disease and lead toxicity have been implicated in hypocalcaemia[41]. Kidney damage leads to increased loss of calcium through increased excretion while lead toxicity is known to cause reduced calcium levels by competing with the metal for binding sites. Again, serum sodium and chloride were found to be higher in occupationally-exposed subjects when compared with the environmentally-exposed and control subjects. This correlated with the blood pressure of these subjects, indicating reduced regulatory functions of the kidney. Some epidemiological studies[31,32,35] have shown association between concentration of lead in the blood and blood pressure, demonstrating hypertension as a cardinal feature of lead nephropathy. Since hypertension is one of the cardinal features of kidney damage, it is expected that all heavy metals incriminated in renal failure can also cause hypertension.

The results also showed that creatinine concentration correlates positively with age in all the groups-occupationally-exposed, environmentally-exposed and control groups. However, though sodium and bicarbonate correlated with age in different groups-environmentally-exposed and occupationally-exposed respectively, the correlation study did not indicate that the effects of these metals were more pronounced in any age group. Worthy of note from the results of this study is the fact that these differences implying impaired kidney function were demonstrated in both male and female subjects, giving the same picture in both occupationally-exposed and environmentally-exposed. This gives the impression that both sexes are equally affected by the heavy metals, both miners and non-miners. And more disturbing is the significant differences in the parameters when environmentally-exposed subjects were compared with the control subjects. Such

significant differences imply that people living within the vicinity but not even working in the mines may eventually develop kidney problems after a long period of exposure. Though good occupational controls and removal of lead from paint, gasoline and other environmental sources in developed countries have made high level of lead exposure required to cause lead nephropathy increasingly rare[10], such cannot be said of developing and resource-disadvantaged countries where legislations, or their enforcements, for control of occupational hazards are rare. The situation with artisanal miners will even be worse. There is enough evidence that combined effects of different heavy metals have cumulative nephrotoxicity[1]. This could be possible in mining communities like Enyigba, given that all the heavy metals studied were significantly higher in both occupationally and environmentally exposed subjects than the controls. Particularly, lead ions can easily cross the blood-brain barrier and therefore very critical during early development when the brain structure is not yet mature. The levels of these toxicants are therefore very critical to the health of infants and children of this community who are now prone to the dangers of lead poisoning in children, characterized by neurological symptoms such as headache, convulsions, ataxia, learning disorders and hyperactive behavior[3]. Unfortunately, there is no documented chemotherapeutic option for the systemic effects of these metals, except chelation and prevention of exposure[1,42] and possibly early detection and withdrawal from the environment. Therefore, inhabitants of areas like Enyigba community must be jealously protected by government legislations, constant public health education and routine medical investigations and advice for miners and the general community to avoid widespread kidney failures. Most important of all these measures is the routine medical investigation as a proactive action against nephrotoxicity. This is very necessary because prevention of kidney diseases induced by exposure to heavy metals should rely heavily on the ability to detect nephrotoxic effects at a stage when they are still reversible or at least before renal function is compromised. Detecting early renal pathology can be easier by use of more sensitive newer biomarkers such as low molecular weight proteins, urinary enzymes and eicosanoids which have shown higher sensitivity and higher negative prediction value than urea and creatinine[35,43]. For instance, exposure to lead has been linked to increased urinary excretion of low molecular weight proteins and lysosomal enzymes[33] and reduced renal synthesis of eicosanoids[35].

CONCLUSION

This study shows that the inhabitants of Enyigba community and possibly other lead-zinc mining communities, especially in the developing and under-developed countries, are predisposed to renal dysfunction. This is irrespective of whether an individual is a miner or not.

SIGNIFICANCE STATEMENT

It is therefore, advocated that the inhabitants of such communities be constantly investigated using more sensitive markers for prompt medical attention. Most importantly, governments of such countries should enact desirable legislations for proper effluent discharge to protect the inhabitants from the toxic effects of these heavy metals. This is in addition to provision of protective measures for the miners.

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