

## ORIGINAL ARTICLE

## LEAD, HYPERTENSION, AND CHRONIC RENAL FAILURE

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**Background:** Chronic kidney disease (CKD), a condition frequently attributed to uncontrolled diabetes and hypertension, has become an economic and public health burden both globally and locally. The present study was designed to investigate the toxic effects of lead and hypertension (HTN) on chronic renal failure (CRF). **Method:** It was a cross-sectional, prospective study conducted in Jinnah Postgraduate Medical Centre, Karachi. A total of 150 adults aged >40 years were included, 50 were diagnosed patients of hypertension, 50 were diagnosed patients of hypertension with chronic renal failure, and 50 were normal healthy individuals. Levels of lead in blood samples of HTN and CRF patients were estimated besides the levels of HbA1c, glucose, urea, creatinine and antioxidant enzymes (SOD, catalase, NO, Glutathione peroxidase) by using kit method. **Results:** Lead levels were higher in HTN and CRF patients compared to controls. Urea, creatine and creatinine clearance levels were high in patients of HTN with CRF. Glucose and HbA1c levels were higher in HTN, and HTN with CRF patients compared to controls. The activity of antioxidant enzymes was decreased in HTN, and HTN with CRF patients. **Conclusion:** Lead exposure with HTN can be a cause of CRF.

**Keywords:** Lead, Hypertension, Diabetes, Renal failure, Antioxidant Enzymes

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## INTRODUCTION

The mammalian kidney is structurally and functionally a complex organ that plays an important role in control and regulation of homeostasis with various re-absorptive, secretory, metabolic and endocrine functions.<sup>1</sup> Chronic kidney disease (CKD), a condition frequently attributed to uncontrolled diabetes and hypertension, has become an economic and public health burden both globally and locally.<sup>2</sup> The term CRF usually means the final stage of chronic kidney disease (CKD) with a decline in glomerular filtration rate (GFR) below 0.25 ml/s. CRF is a worldwide serious health and economic issue with an increasing incidence and prevalence.<sup>3</sup> Hypertension is one of the most important risk factors for cardiovascular and renal diseases. Currently, approximately 1 billion adults worldwide have hypertension, and the prevalence is increasing.<sup>4</sup> Systemic hypertension and glomerular hyper-filtration lead to progressive nephron damage. Effective blood pressure (BP) control delays the progression of renal disease in adults with CKD.<sup>5</sup>

Hypertension develops when vascular endothelial growth factor (VEGF) stimulates production of nitric oxide and prostacyclins in vascular endothelial cells, vasodilatory mechanisms become inhibited, and peripheral vascular resistance increases, leading to increased BP. In addition, there is evidence to suggest that hypertension may result from structural or functional vascular rarefaction caused by inhibition of angiogenic growth factors. Hypertension may also result from decreased glomerular filtration rate and increased sodium and water retention by the kidney, similar to pre-eclampsia associated hypertension.<sup>6</sup>

Several minerals are known to be toxic even in small amount.<sup>7</sup> These elements play important role in various metabolic processes and their deficiency or excess may adversely affect the biochemical functions.<sup>8</sup>

Heavy metals become more concentrated as animals fed on plants. When they reach high levels in the body, heavy metals can be immediately poisonous, or can result in long-term health problems.<sup>9</sup> It may also pose health hazards to the public because of their presence in air, water, food chains as well as to the workers engaged in mining, smelting, alloy, painting, electroplating, pesticides, and the variety of industrial activities.<sup>10</sup> Lead is pervasive chemical that is well known for its toxicity.<sup>11</sup> Exposure to lead can have deleterious effects on multiple organ systems, including the nervous, haematopoietic and renal systems.<sup>12</sup> Clinical studies in industrial workers have shown that development of renal insufficiency after exposure to lead and there have been several cases reports of renal cancer have also been reported.<sup>13</sup> Greater blood lead levels are associated with mortality and deaths from chronic kidney diseases. This association is apparent in the range of blood lead level below 10 µg/dl.<sup>14</sup>

Kidney is one of the prominent sites for intense oxidative processes in the body and is, therefore, extremely vulnerable to free radical-mediated injury.<sup>15</sup> Numerous short-lived and highly reactive oxygen species (ROS) such as superoxide, hydroxyl radical, and hydrogen peroxide are continuously generated. Depending upon concentration, location and intracellular conditions, ROS can cause toxicity or act as signalling molecules. The cellular levels of ROS are controlled by antioxidant enzymes and small molecule antioxidants.<sup>16</sup>

The present study was designed to investigate the toxic effects of lead and hypertension on chronic renal failure.

### MATERIAL AND METHODS

This was a prospective, cross-sectional, comparative study conducted on patients with hypertension, hypertension with CRF, and controls. A total of 150 adults aged >40 years were included, 50 were diagnosed patients of hypertension, 50 were patients of hypertension with chronic renal failure, and 50 were normal healthy individuals. Patients were selected from the areas under heavy water pollution by the toxic metal. The blood samples were collected at Jinnah Postgraduate Medical Centre, and Kidney Centre Karachi.

The subjects were selected after taking written consent, detailed history and examination. Patients suffering from other endocrinal disorders, hepatic disease, alcoholism or drug abuse, and in case of female patients, having pregnancy and using oral contraceptive pills were excluded.

A predefined protocol was used for specimen preparation. Blood was collected in a Gel Barrier Silicone coated Neotube from Nipro Japan. The additive free tubes were kept at room temperature until clotting was complete. Samples were centrifuged at 3,000 rpm for 10 minutes within one hour of collection; serum was separated and stored in aliquots at -20 °C until assayed. Collected samples were analysed in one run.

Plasma glucose was assayed using the glucose oxidase method.<sup>17</sup> Diazyme Direct Enzymatic Haemoglobin A1c (HbA1c)<sup>18</sup> was used in the quantitative determination of HbA1c in human whole blood samples. Urea was assayed enzymatically by the improved Jung method<sup>19</sup> at 520 nm. Creatinine concentration was estimated by Jaffe method<sup>19</sup> at 510 nm. Creatinine clearance (CCr) was calculated from the creatinine concentration in the collected urine sample (UCr), urine flow rate (V), and the plasma concentration (PCr)<sup>19</sup>. Atomic Absorption Spectrophotometer was used as per standard procedure published by the American Public Health Association for the examination of blood samples.<sup>20,21</sup> The SOD<sup>22</sup>, catalase<sup>23</sup>, NO<sup>22</sup> and Glutathione peroxidase<sup>24,25</sup> activities were analysed with Randox kits and were evaluated with a Shimadzu Spectrophotometer.

Data were analysed using SPSS-11. A descriptive analysis of continuous variables was performed. Data on continuous variables were presented as Mean±SD. ANOVA with tukey test were used for continuous variables, and  $p < 0.05$  was considered significant.

### RESULTS

We examined 150 blood samples obtained from different ages and both genders. Many blood samples

had lead concentration higher than the maximum acceptable limit (MAC) of (1.5 µg/dl) established by WHO. Mean of fasting blood sugar (101.3±14.65) and HbA1c (5.6±0.90) in HTN with CRF patients were almost similar to hypertensive and controls ( $p > 0.05$ ).

Mean urea (132.0±28.2) and creatinine (7.8±1.38) in HTN with CRF patients were significantly higher compared to hypertensive and controls ( $p < 0.01$ ). Creatinine clearance (59.6±6.73) in HTN with CRF patients was significantly less compared to hypertensive and controls ( $p < 0.01$ ). Lead was significantly high (12.0±3.80) in HTN with CRF and (11.5±4.65) hypertensive patients compared to controls ( $p < 0.01$ ).

Super-oxide dismutase was significantly less (123.5±16.61) in HTN with CRF and hypertensive (121.9±17.28) compared to controls ( $p < 0.01$ ). Catalase was significantly less (5.4±0.94) in HTN with CRF compared to controls ( $p < 0.01$ ). Glutathione peroxidase was significantly less (46.7±11.66) in HTN with CRF and hypertensive (44.3±9.23) compared to controls ( $p < 0.01$ ). NO was significantly less (12.8±2.92) in HTN with CRF compared to hypertensive and controls ( $p < 0.01$ ) (Table-1).

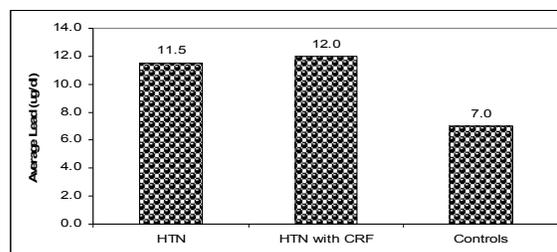
**Table-1: Glycaemic status, renal function, and antioxidant enzymes activity in HTN, HTN with CRF, and controls**

Parameters	Hypertensive	HTN with CRF	Controls	p
<b>Glycaemic status</b>				
Fasting Blood Sugar (mg/dl)	100.5±14.48	101.3±14.65	100.8±15.47	0.957
HbA1c (%)	5.5±0.88	5.6±0.90	5.5±0.94	1.000
<b>Renal Function</b>				
Urea (mg%)	24.2±8.73	132.0±28.2*	22.3±8.49	0.001
Creatinine (mg%)	1.15±0.22	7.8±1.38*	1.12±0.23	0.001
CCr (ml/min)	115.3±13.91	59.6±6.73	108.8±14.36	0.001
Lead (µg/dl)	11.5±4.65	12.0±3.80	7.0±5.11	0.001
<b>Antioxidant enzymes</b>				
Superoxide dismutase (U/ml)	121.9±17.28	123.5±16.61 <sup>o</sup>	204.5±22.68	0.001
Catalase (U/ml)	6.5±1.66	5.4±0.94 <sup>v</sup>	7.1±1.98	0.001
Glutathione peroxidase (µg/Hb)	44.3±9.23	46.7±11.66 <sup>o</sup>	52.1±5.27	0.001
Nitric oxide (µmol/L)	17.6±3.03	12.8±2.92*	18.6±2.98	0.001

\*Significant as compared to Hypertensive and Controls  $p < 0.01$ ,

<sup>o</sup>Significant as compared to Controls  $p < 0.01$

Lead levels in HTN, and HTN with CRF were significantly higher than controls ( $p < 0.01$ ) (Figure-1).



**Figure-1: Lead (µg/dl) in patients and controls**

## DISCUSSION

The results of the present study revealed that hypertensive and chronic renal failure patients have unacceptably high levels of lead in their blood. We have found that some medical and socioeconomic factors like hypertension, diabetes, and hyper-cholesterolemia are also associated with chronic kidney disease (CKD).

Lead poisoning may remain asymptomatic for many years. Major symptoms of lead poisoning are hypertension and neuropathy. Furthermore, chronic lead poisoning may be a cause of chronic renal failure. The design of our study does not enable us to discuss role of lead in the onset of CRF. Determination of such a relationship would require epidemiological studies conducted according to rigorous methodology. A study of incident chronic kidney disease (CKD) cases among lead workers in Sweden failed to find an increased risk of CKD or faster rate of decline in GFR over a 7–9 year follow-up interval.<sup>26</sup>

In our study, the blood lead levels were significantly higher than the control group, hypertensive, and hypertension with CRF patients.

Hypertension is a major risk factor for CKD and can induce several other risk factors. Hypertension is common in older adults and is a known risk factor for incident of heart failure and kidney failure.<sup>27</sup> In our study 97% of blood samples of hypertensive patients with chronic renal failure had lead levels above the levels recommended by WHO.

We found that ‘essential’ hypertensives might well represent cases of chronic Pb intoxication, and that this might explain a certain proportion of those ‘essential’ hypertensives that develop CRF despite good blood pressure control and follow-up of their hypertension. Our results suggest that CRF does not lead to Pb accumulation by itself. If CRF patients exist with chronic Pb poisoning then it is reasonable to think that Pb is the cause of the CRF in those patients even though the source of Pb exposure remains unclear. A number of studies have demonstrated that lead exposures resulting in blood lead levels below 10 µg/dL may cause cognitive dysfunction, neurobehavioral disorders, neurological damage, hypertension and renal impairment.<sup>28</sup>

Even low-level exposures to lead impair cell-mediated immunity by upsetting the balance between Th1- and Th2- like T-lymphocytes which alters cytokine expression. The changes in pro-inflammatory cytokines also play a role in the neurotoxicity of lead.<sup>29</sup> Blood Pb levels are not a suitable basis for the diagnosis of chronic Pb intoxication as they are only an indicator of recent exposure. Lead has long been known to be a renal toxicant. Some recent studies focused on patients with CKD evaluated that greater lead exposure is associated with the loss of kidney function.<sup>14</sup>

The World Health Organization noted that in 2000 approximately 10% of children had a blood lead level of 20 µg/dL or higher and 99% of these children lived in developing countries and that lead exposure accounted for nearly 1% of global burden of disease.<sup>30</sup>

Several factors have been reported to modify the association between blood lead level and kidney function, although the evidence is inconsistent. These include certain genetic polymorphisms, including ALAD, the vitamin D receptor and nitric oxide synthase.<sup>31</sup> One study investigated the association between lead exposure and change over time in renal function. In the NAS cohort, Tsaih *et al*<sup>32</sup> found that the lead-related decline in renal function over a 6-year follow-up interval, specifically the rate of rise in serum creatinine level, was greater in individuals who, at baseline, had diabetes. The studies on lead exposure and renal function in even younger children suggest that higher blood lead levels are associated with increased GFR, suggesting a paradoxical effect that, perhaps, reflects a hyperfiltration phenomenon.<sup>31</sup>

In our study the levels of antioxidant enzymes were in normal limits. Substantial experimental evidence implicates oxidative stress via oxidation-reduction-inactive metal pathways for lead, resulting in increased reactive oxygen species. Recent studies show that oxidative stress takes part in the aetio-pathogenesis of many illnesses. Here, two types of damage may come to play. First, the free oxygen radicals may increase and second, one of the defence mechanisms of the body may be malfunctioning due to the lack of SOD.<sup>33</sup>

## CONCLUSION

Blood lead levels were significantly higher in hypertensive and hypertension with CRF patients than the control group.

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## REFERENCES

1. Sabolic I. Common mechanisms in nephropathy induced by toxic metals. *Nephron Physiol* 2006;104:107–14.
2. Jennette CE, Vupputuri S, Hogan SL, Shoham DA, Falk RJ, Harward DH. Community perspectives on kidney disease and health promotion from at-risk populations in rural North Carolina, USA. *Rural and Remote Health* 2010;10:1–10.
3. Zadrazil J. Aetiology and a clinical picture of chronic renal failure. *Vnitr Lek* 2011;57(7–8):607–13.
4. Chobanian AV. Does it matter how hypertension is controlled? *N Engl J Med* 2008;359(23):2485–8.
5. Wohl E, Trivelli A, Picca S, Litwin M, Peco-Antic A, Zurowska A, *et al*. Strict blood pressure control and progression of renal failure in children. *N Engl J Med* 2009;361(17):1639–50.
6. Rini BI, Cohen DP, Lu DR, Chen I, Hariharan S, Gore ME, *et al*. Hypertension as a biomarker of efficacy in patients with

- metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst* 2011;103:763–73.
7. Lunvongsa S, Tsuboi T, Motomizu S. Sequential determination of trace amount of iron and copper in water samples by flow injection analysis with catalytic spectrophotometric detection. *Anal Sci* 2006;22:169–72.
  8. Wattoo MHS, Kazi TG, Jakhrani MA, Anwar F. Microbiological and elemental status assessments of traces and toxic elements in locally produced glass bottled soft drinks. *J Chem Soc Pak* 2003;25(2):133–8.
  9. Khan MJ, Sarwar S, Khattak RA. Evaluation of River Jehlum water for heavy metals and its suitability for irrigation and drinking purpose at district Muzaffarabad (AK). *J Chem Soc Pak* 2004;26(4):436–42.
  10. Shahtaheri SJ, Khademi M, Golbabaie F, Rahimi FA. Solid phase extraction for monitoring of occupational exposure to Cr (III). *Anal Chem Insights* 2007;2:125–32.
  11. Rahbar MH, White F, Agboatwalla M, Hozhabri S, Luby S. Factors associated with elevated blood lead concentration in children in Karachi, Pakistan. *Bull W Health Organ* 2002;80(10):1–9.
  12. Morales LS, Gutierrez P, Escarce JJ. Demographic and socioeconomic factors associated with blood lead levels among Mexican-American children and adolescents in the United States. *Public Health Rep* 2005;120:448–54.
  13. Fowler BA. Mechanisms of kidney cell injury from metals. *Environ health prospect* 1992;100:57–63.
  14. Bellinger DC. The Protean Toxicities of Lead: New chapters in a familiar story. *Int J Environ Res Public Health* 2011;8:2593–628.
  15. Shiraishi F, Curtis LM, Truong L, Poss K, Visner GA, Madsen K, *et al.* Heme oxygenase-1 gene ablation or expression modulates cisplatin-induced renal tubular apoptosis. *Am J Physiol Renal Physiol* 2002;278:726–36.
  16. Miao L, St. Clair DK. Regulation of superoxide dismutase genes: Implications in diseases. *Free Radic Biol Med* 2009;47(4):344–56.
  17. Tu X, Xie C, Wang F, Chen Q, Zuo Z, Zhang Q, *et al.* Fructus Mume formula in the treatment of type 2 diabetes mellitus: A randomized controlled pilot trial. *Evid Based Complement Alternat Med* 2013:1–8.
  18. Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, Goodall I, *et al.* IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan and Sweden: a method-comparison study. *Clin Chem* 2004;50:166–74.
  19. Owiredu WKBA, Quaye L, Amidu N, Addai-Mensah O. Renal insufficiency in Ghanaian HIV infected patients: need for dose adjustment. *Afr Health Sci* 2013;(1):101–11.
  20. Liu J, Ai Y, McCauley L, Pinto-Martin J, Yan C, Shen X, Needleman H. Blood lead levels and associated socio-demographic factors among preschool children in the south eastern region of China. *Paediatr Perinat Epidemiol* 2012;26(1):61–9.
  21. Alves VN, Borges SSO, Neto WB, Coelho NM. Determination of low levels of lead in beer using solid-phase extraction and detection by flame atomic absorption spectrometry. *J Autom Methods Manag Chem* 2011;2011:464102. doi: 10.1155/2011/464102
  22. Gecit I, Aslan M, Gunes M, Pirincci N, Esen R, Demir H, Ceylan K. Serum prolidase activity, oxidative stress, and nitric oxide levels in patients with bladder cancer. *J Cancer Res Clin Oncol* 2012;138:739–43.
  23. den Besten HM, Effraïmidou S, Abee T. Catalase activity as a biomarker for mild-stress-induced robustness in bacillus weihenstephanensis. *App Environ Microbiol* 2013;79(1):57–62.
  24. Raffa M, Atig F, Mhalla A, Kerkeni A. Decreased glutathione levels and impaired antioxidant enzyme activities in drug-naïve first-episode schizophrenic patients. *Anal Bioanal Chem* 2012;403(2):431–41.
  25. Staimer N, Nguyen TB, Nizkorodov SA, Delfino RJ. Glutathione peroxidase inhibitory assay for electrophilic pollutants in diesel exhaust and tobacco smoke. *Anal Bioanal Chem* 2012;403(2):431–41.
  26. Evans M, Fored CM, Nise G, Beliocco R, Nyren O, Elinder CG. Occupational lead exposure and severe CKD: a population-based case-control and prospective observational cohort study in Sweden. *Am J Kidney Dis* 2010;55: 497–506.
  27. Iyer AS, Ahmed MI, Filippatos GS, Ekundayo OJ, Aban IB, Love TE, *et al.* Uncontrolled hypertension and increased risk for incident heart failure in older adults with hypertension: Findings from a propensity-matched prospective population study. *J Am Soc Hypertens* 2010;4(1):22–31.
  28. Lanphear BP, Dietrich K, Auinger P, Cox C. Cognitive deficits associated with blood lead concentrations <10 microg/dL in US children and adolescents. *Public Health Rep* 2000;115(6):521–9.
  29. Gillis BS, Arbieva Z, Gavin IM. Analysis of lead toxicity in human cells *BMC Genomics* 2012;13:344–62.
  30. Fewtrell, L, Kaufmann, R, Pruss-Ustun A. Lead: Assessing the environmental burden of disease (Environmental Burden of Disease Series No. 2); World Health Organization: Geneva, Switzerland, 2003.
  31. De Burbure C, Buchet JP, Leroyer A, Nisse C, Haguenoer. Renal and neurological effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. *Environ Health Perspect* 2006;115:584–90.
  32. Tsaih SW, Korrick S, Schwartz J, Amarasiriwardena C, Aro A, Sparrow D, Hu H. Lead, diabetes, hypertension, and renal function: The Normative Aging Study. *Environ Health Perspect* 2004;112:1178–82.
  33. Tabakoglu E, Ciftci S, Hatipoglu ON, Altıay G, Caglar T. Levels of superoxide dismutase and malondialdehyde in primary spontaneous pneumothorax. *Mediators of Inflamm* 2004;13(3):209–10.

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