

Original Research Article

Effect of Heavy Metal Exposure on Kidney Histomorphological Features and Function

ABSTRACT

Mining activities near water can lead to health-related problems caused by heavy metal pollution. The objective of the study was to examine kidney histomorphology and function affected by heavy metal exposure, specifically lead (Pb), cadmium (Cd), and mercury (Hg). Using *Rattus norvegicus* as animal model, true experimental study of posttest and control group design were conducted. The diameter and quantity of glomeruli and renal tubules were utilized as measures to evaluate the histomorphological status of the kidney. The kidney function was analyzed using enzymatic assays of blood urea and creatinine levels. The research group was categorized into four subgroups: the control group (C) received distilled water, whereas three intervention groups were administered water polluted with heavy metals (Pb, Cd, Hg) *ad libitum* for a duration of 28 days. Significant differences in histomorphological characteristics of kidney were found between the control and intervention groups using the One Way ANOVA test (glomerular diameter $p = 0,03$, and cortex tubular kidney lumen $p = 0.01$; medulla tubular $p = 0.02$). No significant difference in urea levels ($p = 0.877$) and creatinine levels ($p = 0.294$) between the control and intervention groups. In conclusion, renal histomorphology features of kidney were altered by subchronic exposure to heavy metals, although kidney function remained unchanged.

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INTRODUCTION

Activities by humans have been acknowledged as the major factor contributing to environmental alterations and ecological disruption. One of the major environmental contamination originated from heavy metal constituents, which occur naturally within the ground. The environmental contamination and exposure of heavy metal to human arises from man made activities, which involves food manufacturing, household settings, agriculture, pharmaceutical industry and industrial activities. At the industrial level, heavy metal contamination arises from coal-fueled and nuclear energy facilities, burning of petroleum, microelectronics, high-voltage transmission lines, metal refining, plastics manufacturing, textile, lumber and paper manufacturing facilities ¹⁻³. The extent and duration of exposure to heavy metal contamination by living organisms determine their level of toxicity.⁴

The increased prevalence of heavy metal exposure adversely affects human health. The

exposure of humans to heavy metals as consequence of industrial activities can be observed through a variety of methods, including inhalation, ingestion of contaminated food, and cutaneous absorption may lead to the occurrence of various disorders in both humans and other organisms.^{4,5} With some exception of materials, many of heavy metals are detrimental to the health of biological organisms.⁶ Excessive levels of essential or non-essential metals exposure might result in physiological, morphological or genetic problems.⁷ Arsenic (As), lead (Pb), cadmium (Cd), mercury (Hg) are known to be carcinogenic, exhibit significant toxicity, and cause multiple organ damage.⁸⁻¹⁰ The properties of heavy metals, such as their tendency to accumulate in the human body and their inability to be fully eliminated, leads to several disorder of organ systems.^{5,11,12} Heavy metal poisoning impacts nearly all organ systems, with the central and peripheral nervous system, hematological system, gastrointestinal system, cardiovascular system, and genitourinary system being the most typically affected. Multiple research have indicated links between heavy metals and various disorders, such as cancer development,⁶ metabolic disorder and syndrome^{13,14} and cardiovascular disease¹⁵⁻¹⁷. The World Health Organization (WHO) has included lead (Pb), cadmium (Cd), mercury (Hg) among the major contaminant of heavy metal found in modern world; consequently, the risk human exposure and public health concern to one or more of these contaminants is virtually inevitable.

The kidney is an essential organ that carries out crucial physiological properties, which include the secretion of waste materials like urea, uric acid, and creatinine and active filtering of extra fluid in the body. The kidneys maintain homeostasis of water, acid-base balance, and electrolytes by filtration and reabsorption. Additionally, the kidney secretes hormones that regulate blood pressure, erythropoiesis, and the maturation of vitamin D. However, the kidney is susceptible to damage from various factors including ischemia, diabetes, immune-mediated injury, pharmacological toxicity, and exposure to environmental heavy metals. In the event of toxicity caused by heavy metals, the kidneys are one of the most critical organs affected. Renal disease caused by environmental pollutants and occupationally-linked toxins is a major significant public health concern. The kidney is particularly susceptible to the toxic effects of Pb, Cd, and Hg.^{12,18,19} The novelty shown in this study is to examine the impact of administration of Pb, Cd, and Hg in low dose on the histomorphology of the kidneys and kidney function. This study investigated the subchronic exposure to Pb, Cd, and Hg in animal model of white rats (*Rattus norvegicus*) and whether they alter the renal histomorphological properties and function.

METHODS

An experimental laboratory method with a randomized design was implemented to conduct this research. The research population consisted of white rats, aged 2 to 6 months and weighing between 250 and 300 grams. The study subjects consisted of 24 male Wistar strain *Rattus Norvegicus* rats sourced from the Animal Laboratory of the Faculty of Medicine and Health Sciences, Lambung Mangkurat University, South Kalimantan, Indonesia. The Federer formula determines the sample size, and minimal number of samples for 4 group in each group is 5-6 rats. The exclusion criteria of this study was rats that die during the acclimatization phase and heavy metal induction process or looked ill after 3 days of induction. A total of twenty four rats is further divided into four groups: 1) Rats given unrestricted access to distilled water as Control group (C); 2) Rats given water contaminated with Pb (0, 01 mg / l = 0.006 mg / kgBW) as Group P1; 3) Rats given water contaminated with Cd (0.003 mg / l = 0.018 mg / kgBW) as Group P2 and; 4) Rats given water contaminated with Hg (0.001 mg/l = 0.0006 mg/kgBW) ad Group P3. On the 28th day, rats in all groups were euthanized.¹⁸ This dosage determination is converted from the SNI safety standard (minimum limit of heavy metals allowed in drinking water).

Research Tools and Materials

Instruments for necropsy were utilized for the collection of kidney tissue samples. Kidney tissue was then made into histological slide preparations using the paraffin method and hematoxylin-eosin (HE) staining technique. Slides were then observed using binocular microscope (OLYMPUS®) and were photographed using the Optilab® View software. The diameter of the glomerulus and renal tubules was measured using Image Raster software. Urea (BUN) kit (UREFSR-0, MERIL®) and creatinine kits (CREFSR-01, MERIL®) were utilized to assess renal function. Quantitative determination of urea and creatinine were measured using ELISA method.

Research Procedure

Acclimatization stage

The acclimatization of the rats was conducted for one week prior to the study in order to ensure uniform physical and psychological conditions. The rats received standard diet, and daily behavioral and physical assessments were performed to monitor any changes in each rat. On the eighth day, this stage was completed.

Intervention and termination stage

The control group (C) was administered aquadest *ad libitum*, while the intervention group (P1, P2 and P3) was orally administered heavy metal-contaminated water of Pb, Cd, or Hg through sondage. This stage was performed for 28 days. On the 29th day, the rats were nocturnally fed and subsequently euthanized the next day. Lethal dose of ketamine injection was injected to euthanized the rats. The blood samples were collected, followed by a postmortem examination of the kidneys. Kidney tissue specimens were subsequently collected for histological examination. Blood samples were obtained for the kidney function test examination.

Histopathological preparation

Histopathological examination was performed as previously described (19). A 10% neutral buffered formalin (NBF) solution was used to store 24 rat kidney samples obtained for each research groups. Samples were then made into histopathological preparations. Once the tissues had been dehydrated, they were embedded in paraffin. Then, paraffin-embedded fragment sections of 4–5 µm were obtained using rotary microtome slicing. The histological properties of the kidney were visualized under an optical microscope by previously mounting the sections on glass slides and staining them with hematoxylin and eosin. The diameter of the glomerulus and the lumen of the tubules in both the cortex and medulla were observed microscopically using an Optilab Camera. The observation was within a field of vision of 5 × 5 mm, up to five times the field of view. Measurement of glomerulus and renal tubule diameter was done using the following formula:(21)

Average diameter of glomerulus (DG):

$$\frac{\sum \text{average diameter of glomerulus in 5 fields of view}}{\sum \text{glomerulus in 5 fields of view}}$$

Average diameter of tubular lumen (TL):

$$\frac{\sum \text{Average diameter of tubular lumen in 5 fields of view}}{\sum \text{Tubular in 5 fields of view}}$$

Blood serum collection

On the 29 th day, the rats were sedated, and 10 ml of blood was drawn from the inferior vena cava to obtain serum, which later was utilized to assess and renal function by analyzing urea and creatinine levels. The serum was allowed to clot for 10–20 min at room temperature, followed by centrifugation at 2000–3000 RPM for 20 minutes at 2–8°C. The supernatant was then collected, ensuring no sediment was included, to carry out the assay.²⁰

ELISA examination

Kidney damage induced by heavy metals mixture were assessed through measurement of serum urea and creatinine. The levels of urea and creatinine were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits. Serum urea and creatinine activity were determined using commercial kits Medik Bio Urea Assay Kit cat.No MDB0057 and Medik Bio Creatinine ELISA Kit cat.No MDB0058). The manufacturer's guidelines were meticulously adhered to

during the testing procedure.²⁰

Data Analysis

Histomorphological features (glomerular diameter and tubular kidney lumen) and kidney function (urea and creatinine levels) were assessed using the Kruskal-Wallis test and one-way ANOVA. A post hoc of Tukey's HSD test was carried out if the hypothesis was accepted. The confidence level used in the study was 95%, and p value of < 0.05 was considered statistically significant.

RESULT AND DISCUSSION

Based on the results of the research carried out, the following were obtained:

Kidney Histomorphological

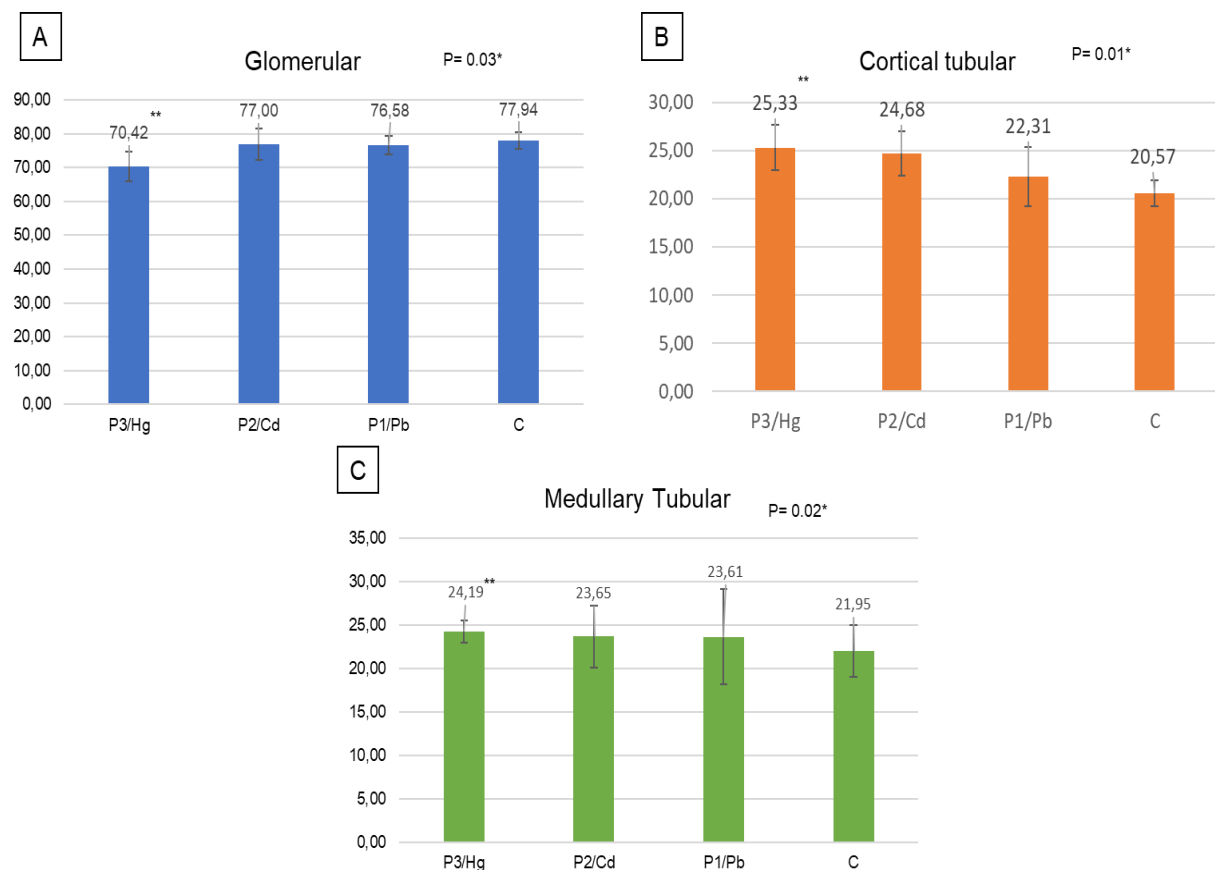


Figure 1. A) Glomerular; B) Cortical Tubular; C) Medullary Tubular Lumen Size (μm) in control (C) and intervention groups (P1, P2, P3).

Note: * significant One Way ANOVA; compared with the control group; ** significant Tukey's HSD test; compared with all groups

Figure 1 demonstrated a statistically significant reduction in the diameter of the glomerulus in the intervention group relative to the control group (p value = 0.03). The Tukey test indicated that exposure to Hg significantly reduces the width of the glomerulus more than in the administration of Cd and Pb.

Figure 2 shows the difference in the size of the glomerular diameter glomerulus between the control and intervention groups. The intervention group showed a reduction in glomerular size compared to the control group (p=0.03) and the Hg intervention group showed the most reduction in glomerular size among others.

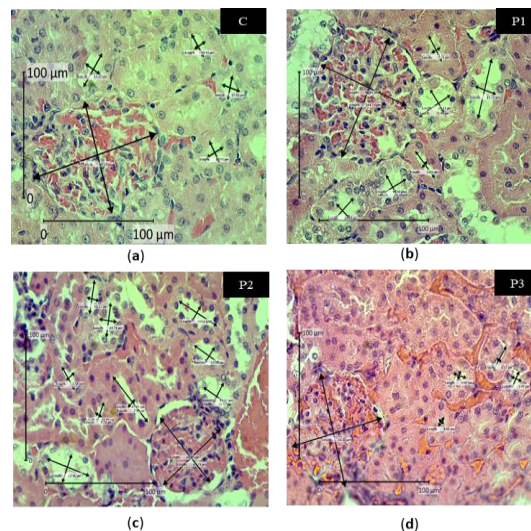


Figure 2. Microscopic analysis of glomerular diameter on: A) control group (C) and : B,C,D) intervention groups (P1, P2, and P3). Black arrow: shortest diameter; Red arrow: longest diameter. HE staining. 400x Magnification

Figure 3a showed the size of the tubular lumens of the cortex and the medulla of the kidney tubules between control and intervention groups. The study results showed that there was thinning of the tubule wall as indicated by the widening of the lumen of the cortex and medulla tubules in the intervention group compared to the control group ($p=0.01$; $p=0.02$ respectively) and the Hg intervention group showed the most thinning in tubule wall compared to the administration of Cd and Pb.

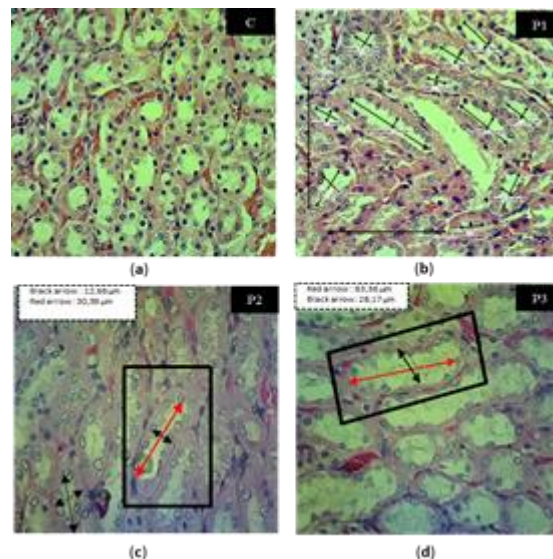


Figure 3. Microscopic analysis of medullary renal tubular lumen on: A) control group (C) and : B,C,D) intervention groups (P1,P2, and P3). Black arrow: shortest diameter; Red arrow: longest diameter. HE staining. 400x Magnification

The renal histopathology examination in our study revealed significant alterations of the organ. Exposure to Pb, Cd and Hg in rats result in kidney histopathological alterations consist of shrinkage of the glomerulus and tubules due to the process of necrosis. Our study result was in line with the study of Cd intoxication by Z. Gattea Al-Rikabi et al.²¹, which concluded histopathological changes of the kidneys in experimental animal model including severe vascular

degeneration and necrosis of renal tubules with glomerular deterioration. Amin et al²² stated that the administration of Pb to rats can cause changes in the microscopic features of the kidneys because it leads to disruption of the anti-oxidative enzyme system, organ function, and lipid membranes of the cell causing oxidative stress. Research by Bas et al found that the administration of Pb and Cd for 28 days can cause histopathological changes in the kidneys.²³ The toxic effects of combined heavy metal (Cd, Pb, Hg) exposure on kidneys, as stated by Singh et al²⁴, can structurally damage the kidney tissue and even alter the excretory function. It was found the inflammation was further exacerbated by necrosis, glomerular injury, oxidative stress, and cell death.

The mechanism of microscopic morphological changes of the kidneys caused by heavy metals contamination were associated with oxidative stress, glomerular damage, necrosis, cell death and further exacerbation of the inflammation.^{25,26} There are several other explanations for damage to the kidney structure by heavy metals. In the administration of Cd, the kidney damage starts from the occurrence of cadmium ingestion as ROS which trigger oxidative stress and inflammation that causes intracellular changes, via endoplasmic reticulum stress, mitochondrial dysfunction, disturbances in cell adhesion and cell transporters with result in cell injury and cell death (podocytes, tubule epithelial cells and vascular endothelial cells).²⁶⁻²⁸ The toxic effects of Hg on kidney is mostly affecting renal tubule epithelial cells, which further disrupt renal function. Exposure to Hb on cultured proximal tubular cells results in substantial cellular modifications. The most significant alterations including mitochondrial dysfunction, cytoskeletal rearrangements, increased oxidative stress and intracellular calcium, and reduced cellular viability.²⁸⁻³¹ In Lead (Pb) poisoning, ROS (Reactive oxygen species) such as hydroperoxide, hydrogen peroxide, and singlet oxygen are produced, which further leads to oxidative stress and cellular damage. Oxidative stress causes cell and tissue destruction, which increases the likelihood of adverse health outcomes including renal dysfunction and toxicity.³² Lipid peroxidation is induced by elevated oxidative stress, which leads to cell membrane injury. The accumulation of lead in the proximal renal tubular lining cells and the formation of inclusion bodies, such as the lead-protein complex, will result in proximal tubular dysfunction. Kidney-specific proteins function as receptors and facilitate interactions with DNA in renal proximal tubular cells. In case of lead contamination, it binds with kidney-specific protein and induces carcinogenesis. Renal plasma excretion and plasma renin activity were also influenced by lead exposure. The reabsorption of sodium, a critical renal process, is impaired by lead toxicity in mitochondria, resulting in an insufficient supply of ATP, subsequently increase sodium excretion in the urine.^{32,33}

Kidney Function

The creatinine level data was analyzed using Kruskal-Wallis. The one-way ANOVA test was applied for normally distributed urea level data. The following data were obtained:

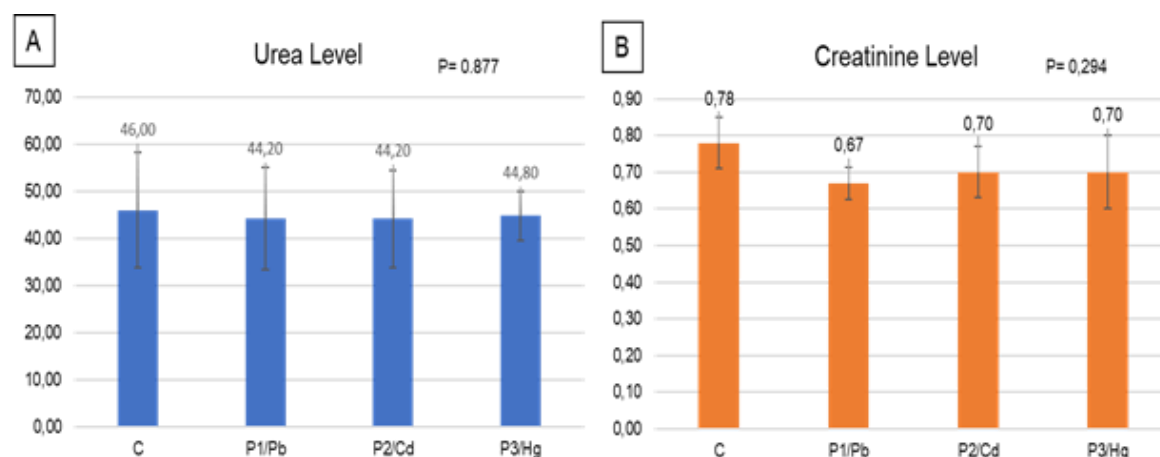


Figure 4. Kidney function of A) Urea Level dan B) Creatinine Level in control (C) and intervention groups (P1, P2, P3)

Note: * $p < 0.05$ (One Way ANOVA) and ** $p < 0.05$ (Kruskal Wallis) compared with the control group

As shown in Figure 4, there was no statistically significant difference in renal function parameters of urea (p value=0,877) and creatinine (p -value=0,294) between the control and intervention groups. However, the intervention group exposed to heavy metals Pb, Cd, and Hg exhibited a tendency of reduced urea and creatinine levels in comparison to the control group. This indicates kidney dysfunction because both tests are nephrotoxicity markers. The kidneys eliminate urea and creatinine, which are two of the remaining metabolic products. There was no statistically significant difference of urea and creatinine levels between the three intervention groups. Based on these data, it can be concluded that 28 days of heavy metal administration has no impact on kidney function alteration.

The results of this study are in accordance to other research related to the impact small doses and subchronic exposure of heavy metals on kidney function^{34–38}. Andjelkovic et al³⁴ in their present work found that the impact of heavy metal toxicity on the kidneys is highly dependent on the dose and duration of administration. There is a strong correlation between dose and markers of oxidative stress and kidney organ damage. Study by Jarovac et al³⁵ showed that low subacute lead exposure did not significantly impact the serum nephrotoxicity markers of creatinine and urea levels. The kidneys eliminate urea and creatinine, which are two of the remaining metabolic products. Typically, the bloodstream contains only a tiny amount of creatinine and urea. The mercuric chloride ions are estimated to have a total body half-life of approximately 30–60 days. This pathomechanism is one of the reasons for the low detection of urea and mercury creatinine levels in the blood.^{36–39} Reduced urea and creatinine levels are associated with diseases that diminish or decreased urea production, including tubular necrosis, advanced liver disease, and insufficient protein intake.⁴⁰

Pathomechanism Of Changes In Histomorphology and Kidney Function Due To Exposure to Lead (Pb), Cadmium (Cd) and Mercury (Hg)

Acute tubular damage, proteinuria, and chronic kidney disease are the primary forms of kidney injury caused by heavy metals.^{18,41} Interstitial nephritis, cortical atrophy, and proximal tubular injury have been observed in renal biopsies following Pb, Cd, and Hg poisoning. Intranuclear inclusion bodies have also been observed in some cases. Histopathological examinations of kidney exposed to heavy metals have revealed membranous nephropathy, which is characterized by thickened glomerular basement membrane, immunoglobulin deposits, and tubulointerstitial injury.^{42,43} Research on low-level environmental exposure has reported correlations between the concentrations of Pb, Cd, and Hg in blood or urine and a variety of biomarkers of kidney function. Cross-sectional studies conducted in the general population have reported correlations between estimated glomerular filtration rate (eGFR) and blood lead (Pb). Regarding Cd, studies have demonstrated that the excretion of low molecular weight proteins is increased in response to Cd levels in the blood or urine, which suggests that renal tubular dysfunction is responsible. Regarding Hg, Studies have demonstrated elevated excretion of the enzyme N-acetyl glucosaminidase, indicating a possible adverse effect on the kidney.^{41,44}

The toxicity of biological systems is induced by exposure to heavy metals and environmental pollution through the generation of ROS and the bonding to sulfhydryl groups. This leads to the inactivation of essential macromolecules, resulting in oxidative stress and a reduction of antioxidants. Upon exposure and entry of heavy metals into the body, multiple events occur, these include specific organ dysfunctions, metabolic abnormalities, altered hormones, congenital disorder, immune system dysfunction, and carcinogenesis.^{9,15,41} Upon entering the body, heavy metals can bind to proteins, lipids, and nucleic acids. Binding to enzymes and proteins often happens via thiol (–SH) groups, resulting in modifications of cysteine residues within proteins. The interaction of heavy metals with the sulfhydryl group (–SH) in proteins can lead to protein inactivation, which may disturb the intracellular redox state. Thus, an inadequate antioxidant defense facilitates the progression of cellular damage. In the complexation of heavy metals with thiol-containing proteins, the ligands are amino acids that possess the –SH functional group. Free radicals, particularly ROS and RNS, can be generated by toxic metals, which can induce oxidative stress. For example, it has been shown that heavy metals produce superoxide ($O_2^{\cdot-}$), oxygen (O_2), hydrogen peroxide (H_2O_2), nitric oxide ($NO^{\cdot}$), and peroxy

(ROO[•]) radicals. Heavy metal exposure significantly reduces antioxidant measures GPx, CAT, SOD, GST, and GSH, while concurrently increasing oxidative metrics MDA and H₂O₂. It is hypothesized that the detrimental effects of heavy metals on the human body are linked to the increased production of reactive oxygen species (ROS). This leads to a decrease in the activity of antioxidant enzymes, including catalase, glutathione peroxidase, and SOD. Additionally, the high affinity of heavy metals for –SH groups can result in both a decrease in glutathione peroxidase activity and interference with the intracellular signaling of numerous receptors.⁴⁵

Cadmium toxicity is induced either directly through the production of reactive oxygen species (ROS) or indirectly through the depletion of cellular antioxidants. Prolonged cadmium exposure can cause renal impairment in animals by damaging the proximal tubules.⁴⁴ Cadmium promotes cellular death in various organs by influencing transcription factors and regulating their target genes.⁴⁵ Cd may impair mitochondria by obstructing the mitochondrial electron transport chain. Additionally, Cd induces the accumulation of mitochondrial reactive oxygen species (ROS), an increase in ion permeability in the inner membrane, and a decrease in mitochondrial membrane potential, all of which contribute to cell apoptosis. Additional hypothesized mechanisms of Cd toxicity include ER stress-mediated apoptosis, DNA damage and inhibition of certain DNA repair enzymes, and epigenetic alterations that result in altered gene expression. This increase may lead to DNA damage and disruption of transcription and translation processes.^{15,45}

Toxicity of mercury (Hg) varies with its chemical forms, dosage, and rate of exposure. The most nephrotoxic forms of mercury are predominantly inorganic species. Mercuric ions (Hg²⁺) rapidly accumulate in renal proximal tubule cells, which have specific transport systems involved in the handling of Hg²⁺. Numerous *in vivo* and *in vitro* investigations have demonstrated that Hg²⁺ S-conjugates of small endogenous thiols represent the principal transportable forms of mercury within the kidneys. Mercury can cause cell injury through different mechanisms such as the formation of reactive oxygen species, lipid peroxidation, alteration of protein synthesis and metabolic disorders, by binding and interacting with complexes of protein and non-protein sulfhydryl, mitochondrial dysfunction, disruption of cytoskeleton, cell apoptosis and necrosis. Hg²⁺ has also been implicated in the buildup of inflammatory components and the development of autoimmunity.^{46,47}

Lead-induced renal injury is characterized by a variety of toxicodynamic mechanisms. Ca²⁺ can be competed with by Pb²⁺, which can disrupt calcium homeostasis. Consequently, the release of Ca²⁺ from mitochondria is induced, which leads to the opening of the mitochondrial transitional pore. This, in turn, results in the generation of reactive species, the accumulation of oxidative stress, and the alteration of lipid metabolism, as well as total mitochondrial damage. Proximal tubules are more susceptible to apoptosis following cellular injury induced by Pb than other cells. Another theory suggests that Pb compromises the integrity of cell–cell junctions (tight junctions) and alters cellular structure. Altered polarity and vectorial transport of epithelial cells may result from atypical cell–cell junction structures due to diminished renal proximal tubule lumen and microvilli loss.⁴⁷ The authors need to mention the strengths and the limitation of the study, as well as potential clinical implications of the findings.

CONCLUSION

After subchronic treatment, exposure to heavy metals (Pb, Cd, and Hg) results in changes in kidney histomorphology without affecting kidney function. The authors need to propose the ideas for the next studies

AUTHOR'S CONTRIBUTION STATEMENT

The contribution of each author are: FU & IY: wrote entire original draft; A: contributed to methodology design and data analysis; IM & SK: provided data for discussion and data analysis; AA, MAA & SSB: data analysis and manuscript editing.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest related to the research, authorship, or publication of this article.

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REFERENCES

1. Javaid A, Akbar I, Javed H, Khan U, Iftikhar H, Zahra D, et al. Role of Heavy Metals in Diabetes: Mechanisms and Treatment Strategies. *Crit Rev Eukaryot Gene Expr* [Internet]. 2021;31(3):65–80. Available from: <https://doi.org/10.1615/CritRevEukaryotGeneExpr.2021037971>
2. Ali SS, Elsamahy T, Al-Tohamy R, Zhu D, Mahmoud YAG, Koutra E, et al. Plastic wastes biodegradation: Mechanisms, challenges and future prospects. *Sci Total Environ* [Internet]. 2021;780:146590. Available from: <https://doi.org/10.1016/j.scitotenv.2021.146590>
3. Ali SS, Abdelkarim EA, Elsamahy T, Al-Tohamy R, Li F, Kornaros M, et al. Bioplastic production in terms of life cycle assessment: A state-of-the-art review. *Environ Sci Ecotechnology* [Internet]. 2023;15:100254. Available from: <https://doi.org/10.1016/j.eset.2023.100254>
4. Sarker A, Masud MA Al, Deepo DM, Das K, Nandi R, Ansary MWR, et al. Biological and green remediation of heavy metal contaminated water and soils: A state-of-the-art review. *Chemosphere*. 2023 Aug;332:138861.
5. Ali H, Khan E, Ilahi I. Environmental Chemistry and Ecotoxicology of Hazardous Heavy Metals: Environmental Persistence, Toxicity, and Bioaccumulation. *J Chem* [Internet]. 2019;2019(1):6730305.
6. Negahdari S, Sabaghan M, Pirhadi M, Alikord M, Sadighara P, Darvishi M, et al. Potential Harmful Effects of Heavy Metals as a Toxic and Carcinogenic Agent in Marine Food-An Overview. *Egypt J Vet Sci*. 2021;52(3):379–85.
7. Mitra S, Chakraborty AJ, Tareq AM, Emran T Bin, Nainu F, Khusro A, et al. Impact of heavy metals on the environment and human health: Novel therapeutic insights to counter the toxicity. *J King Saud Univ - Sci* [Internet]. 2022;34(3):101865. Available from: <https://doi.org/10.1016/j.jksus.2022.101865>
8. Abd Elnabi MK, Elkaliny NE, Elyazied MM, Azab SH, Elkhailifa SA, Elmasry S, et al. Toxicity of Heavy Metals and Recent Advances in Their Removal: A Review. *Toxics*. 2023;11(7).
9. Balali-Mood M, Naseri K, Tahergorabi Z, Khazdair MR, Sadeghi M. Toxic Mechanisms of Five Heavy Metals: Mercury, Lead, Chromium, Cadmium, and Arsenic. *Front Pharmacol* [Internet]. 2021;12:643972. Available from: <https://doi.org/10.3389/fphar.2021.643972>
10. Vizuete J, Pérez-López M, Míguez-Santián MP, Hernández-Moreno D. Mercury (Hg), Lead (Pb), Cadmium (Cd), Selenium (Se), and Arsenic (As) in Liver, Kidney, and Feathers of Gulls: A Review. *Rev Environ Contam Toxicol* [Internet]. 2019;247:85–146. Available from: https://doi.org/10.1007/398_2018_16
11. Jyothi NR. Heavy Metal Sources and Their Effects on Human Health. In: Nazal MK, Zhao H, editors. *Heavy Metals* [Internet]. Rijeka: IntechOpen; 2020. Available from: <https://doi.org/10.5772/intechopen.95370>
12. Yan LJ, Allen DC. Cadmium-induced kidney injury: Oxidative damage as a unifying mechanism. *Biomolecules*. 2021;11(11).
13. Wen W-L, Wang C-W, Wu D-W, Chen S-C, Hung C-H, Kuo C-H. Associations of Heavy Metals with Metabolic Syndrome and Anthropometric Indices. *Nutrients* [Internet]. 2020 Sep;12(9). Available from: <https://doi.org/10.3390/nu12092666>
14. Kang P, Shin HY, Kim KY. Association between dyslipidemia and mercury exposure in adults. *Int J Environ Res Public Health*. 2021;18(2):1–10.
15. Haidar Z, Fatema K, Shoily SS, Sajib AA. Disease-associated metabolic pathways affected by heavy metals and metalloids. *Toxicol reports* [Internet]. 2023;10:554–70. Available from: <https://doi.org/10.1016/j.toxrep.2023.04.010>
16. Sevim Ç, Doğan E, Comakli S. Cardiovascular disease and toxic metals. *Curr Opin Toxicol* [Internet]. 2020;19:88–92. Available from: <https://www.sciencedirect.com/science/article/pii/S2468202020300061>
17. Obeng-Gyasi E, Ferguson AC, Stamatakis KA, Province MA. Combined effect of lead exposure

- and allostatic load on cardiovascular disease mortality—A preliminary study. *Int J Environ Res Public Health*. 2021;18(13).
18. Onan E, Ulu S, Güngör Ö. Heavy Metals and Kidney. *Turkish J Nephrol*. 2024;33(3):244–51.
 19. Jalili C, Kazemi M, Cheng H, Mohammadi H, Babaei A, Taheri E, et al. Associations between exposure to heavy metals and the risk of chronic kidney disease: a systematic review and meta-analysis. *Crit Rev Toxicol* [Internet]. 2021;51(2):165–82. Available from: <https://doi.org/10.1080/10408444.2021.1891196>
 20. Kouam AF, Masso M, Kouoh FE, Fifen R, Njingou I, Tchana AN, et al. Hydro-ethanolic extract of *Khaya grandifoliola* attenuates heavy metals-induced hepato-renal injury in rats by reducing oxidative stress and metals-bioaccumulation. *Heliyon*. 2022;8(11).
 21. Al-Rikabi GZ, Abbas AH, Oudah KH, Nassir SH, Ali SA. Histopathological Study of Liver and Kidney Tissues in C57 Mice via Chronic Exposure to Cadmium and Zinc. *Arch Razi Inst*. 2021;76(5):1183–90.
 22. Amin I, Hussain I, Rehman MU, Mir BA, Ganaie SA, Ahmad SB, et al. Zingerone prevents lead-induced toxicity in liver and kidney tissues by regulating the oxidative damage in Wistar rats. *J Food Biochem*. 2021 Mar;45(3):e13241.
 23. Baş H, Apaydın FG, Kalender S, Kalender Y. Lead nitrate and cadmium chloride induced hepatotoxicity and nephrotoxicity: Protective effects of sesamol on biochemical indices and pathological changes. *J Food Biochem*. 2021;45(7):1–13.
 24. Singh D, Bist P, Choudhary S. Co-exposure to multiple heavy metals and metalloid induces dose dependent modulation in antioxidative, inflammatory, DNA damage and apoptotic pathways progressing to renal dysfunction in mice. *Environ Toxicol Pharmacol*. 2024 Oct;111:104537.
 25. Mishra M, Nichols L, Dave AA, Pittman EH, Cheek JP, Caroland AJV, et al. Molecular Mechanisms of Cellular Injury and Role of Toxic Heavy Metals in Chronic Kidney Disease. *Int J Mol Sci*. 2022;23(19).
 26. Barregard L, Sallsten G, Lundh T, Mölne J. Low-level exposure to lead, cadmium and mercury, and histopathological findings in kidney biopsies. *Environ Res*. 2022;211(December 2021).
 27. Tubsakul A, Sangartit W, Pakdeechote P, Kukongviriyapan V, Apaijit K, Kukongviriyapan U. Curcumin Mitigates Hypertension, Endothelial Dysfunction and Oxidative Stress in Rats with Chronic Exposure to Lead and Cadmium. *Tohoku J Exp Med*. 2021 Jan;253(1):69–76.
 28. Fang J, Xie S, Chen Z, Wang F, Chen K, Zuo Z, et al. Protective Effect of Vitamin E on Cadmium-Induced Renal Oxidative Damage and Apoptosis in Rats. *Biol Trace Elem Res*. 2021 Dec;199(12):4675–87.
 29. Gao Z, Wu N, Du X, Li H, Mei X, Song Y. Toxic Nephropathy Secondary to Chronic Mercury Poisoning: Clinical Characteristics and Outcomes. *Kidney Int Reports*. 2022;7(6):1189–97.
 30. Vieira JV dos A, Marques VB, Vieira LV, Crajoinas R de O, Shimizu MHM, Seguro AC, et al. Changes in the renal function after acute mercuric chloride exposure in the rat are associated with renal vascular endothelial dysfunction and proximal tubule NHE3 inhibition. *Toxicol Lett*. 2021;341:23–32.
 31. Han B, Lv Z, Han X, Li S, Han B, Yang Q, et al. Harmful Effects of Inorganic Mercury Exposure on Kidney Cells: Mitochondrial Dynamics Disorder and Excessive Oxidative Stress. *Biol Trace Elem Res*. 2022 Apr;200(4):1591–7.
 32. Rojas-Franco P, Franco-Colín M, Torres-Manzo AP, Blas-Valdivia V, Thompson-Bonilla MDR, Kandir S, et al. Endoplasmic reticulum stress participates in the pathophysiology of mercury-caused acute kidney injury. *Ren Fail*. 2019 Nov;41(1):1001–10.
 33. Collin MS, Venkatraman SK, Vijayakumar N, Kanimozhi V, Arbaaz SM, Stacey RGS, et al. Bioaccumulation of lead (Pb) and its effects on human: A review. *J Hazard Mater Adv* [Internet]. 2022;7(May):100094. Available from: <https://doi.org/10.1016/j.hazadv.2022.100094>
 34. Andjelkovic M, Buha Djordjevic A, Antonijevic E, Antonijevic B, Stanic M, Kotur-Stevuljevic J, et al. Toxic {Effect} of {Acute} {Cadmium} and {Lead} {Exposure} in {Rat} {Blood}, {Liver}, and {Kidney}. *Int J Environ Res Public Health*. 2019 Jan;16(2):274.
 35. Javorac D, Antonijević B, Anđelković M, Repić A, Bulat P, Djordjevic AB, et al. Oxidative stress,

- metallomics and blood toxicity after subacute low-level lead exposure in Wistar rats: Benchmark dose analyses. *Environ Pollut*. 2021 Dec;291:118103.
36. Caragea G, Vărzaru AC, Avram O, Macovei R, Costea A, Popescu DM, et al. An overview of the complications of acute and chronic mercury exposures. Past, present and future. *Rom J Mil Med*. 2021;124(4):411–9.
 37. Wu YS, Osman AI, Hosny M, Elgarahy AM, Eltaweil AS, Rooney DW, et al. The Toxicity of Mercury and Its Chemical Compounds: Molecular Mechanisms and Environmental and Human Health Implications: A Comprehensive Review. *ACS Omega*. 2024;9(5):5100–26.
 38. Cappelletti S, Piacentino D, Fineschi V, Frati P, D'Errico S, Aromatario M. Mercuric chloride poisoning: symptoms, analysis, therapies, and autoptic findings. A review of the literature. *Crit Rev Toxicol* [Internet]. 2019;49(4):329–41. Available from: <https://doi.org/10.1080/10408444.2019.1621262>
 39. Posin SL, Kong EL, Sharma S. Mercury Toxicity. In *Treasure Island (FL)*; 2025.
 40. Peng R, Liu K, Li W, Yuan Y, Niu R, Zhou L, et al. Blood urea nitrogen, blood urea nitrogen to creatinine ratio and incident stroke: The Dongfeng-Tongji cohort. *Atherosclerosis* [Internet]. 2021;333:1–8. Available from: <https://doi.org/10.1016/j.atherosclerosis.2021.08.011>
 41. Nordberg G, Costa M. Handbook on the Toxicology of Metals, Vol I. 2021. 485–506 p.
 42. Tai YT, Chou SH, Cheng CY, Ho C Te, Lin HC, Jung SM, et al. The preferential accumulation of cadmium ions among various tissues in mice. *Toxicol Reports* [Internet]. 2022;9(January):111–9. Available from: <https://doi.org/10.1016/j.toxrep.2022.01.002>
 43. Feng X, Jin X, Zhou R, Jiang Q, Wang Y, Zhang X, et al. Deep learning approach identified a gene signature predictive of the severity of renal damage caused by chronic cadmium accumulation. *J Hazard Mater* [Internet]. 2022;433(December 2021):128795. Available from: <https://doi.org/10.1016/j.jhazmat.2022.128795>
 44. Ellingsen DG, Efskind J, Berg KJ, Gaarder PI, Thomassen Y. Renal and immunological markers for chloralkali workers with low exposure to mercury vapor. *Scand J Work Environ Heal*. 2000;26(5):427–35.
 45. Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ. Heavy metal toxicity and the environment. *Exp Suppl* [Internet]. 2012;101:133–64. Available from: https://doi.org/10.1007/978-3-7643-8340-4_6
 46. Hazelhoff MH, Torres AM. Effect of erythropoietin on mercury-induced nephrotoxicity: Role of membrane transporters. *Hum Exp Toxicol*. 2021 Mar;40(3):515–25.
 47. Rana MN, Tangpong J, Rahman MM. Toxicodynamics of Lead, Cadmium, Mercury and Arsenic- induced kidney toxicity and treatment strategy: A mini review. *Toxicol Reports* [Internet]. 2018;5(May 2017):704–13. Available from: <https://doi.org/10.1016/j.toxrep.2018.05.012>.