Nephrotoxic Effects of Varying Lead Acetate Doses on Kidney Biochemical Markers and Histology in Adult Male Rats.

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ABSTRACT

Background: Lead is a non-essential, persistent environmental toxicant with no known beneficial biological role, and the kidney remains one of its principal target organs. Despite decades of research, the relationship between oral lead acetate dose and the magnitude of renal biochemical and structural injury continues to be refined. **Objective**: This study evaluated the dose-dependent effects of orally administered lead acetate on serum renal function biomarkers and kidney histoarchitecture in adult male Wistar rats. **Methods**: Twenty adult male Wistar rats (150–200 g) were randomly allocated into four groups (n = 5): a distilled-water control and three treatment groups receiving lead acetate at 100, 200, or 400 mg/kg body weight by oral gavage daily for 21 days. Serum urea, creatinine, and uric acid were assayed, and kidney sections were processed for haematoxylin and eosin (H&E) histology. Data were analysed by one-way ANOVA with Duncan's Multiple Range Test ($p < 0.05$). **Results**: Serum urea and creatinine were numerically highest in the 400 mg/kg group, consistent with a decline in glomerular filtration rate at high-dose exposure, while the 200 mg/kg group showed comparatively modest deviation from control. Serum uric acid was significantly elevated in both the 100 mg/kg and 400 mg/kg groups relative to control, indicating that renal stress was detectable even at the lowest dose tested. Histopathology revealed a clear dose-dependent gradient, progressing from preserved glomerular and tubular architecture in the control group to mild glomerular shrinkage and tubular dilation at 100 mg/kg, moderate glomerular collapse with inflammatory infiltration at 200 mg/kg, and severe glomerular distortion, haemorrhage, and extensive interstitial inflammation at 400 mg/kg. **Conclusion**: Subacute oral lead acetate exposure produces dose-dependent biochemical and morphological nephrotoxicity in Wistar rats, with serum uric acid emerging as a sensitive early indicator of renal injury that precedes overt elevation of urea and creatinine. These findings reinforce the need for renal biomonitoring in lead-exposed populations and support continued evaluation of nephroprotective strategies.

Keywords: Lead acetate; nephrotoxicity; Wistar rats; renal biomarkers; histopathology; oxidative stress; heavy metal toxicity

INTRODUCTION

Lead (Pb) is a non-essential, naturally occurring heavy metal that has no known physiological function in mammalian biology, yet it remains one of the most pervasive environmental and occupational contaminants worldwide [3]. Its continued presence in soil, water, dust, and consumer products stems from legacy uses such as leaded paints and petrol, as well as ongoing activities including mining, smelting, battery manufacturing, and informal electronic-waste recycling [14, 26]. Once absorbed, lead is poorly excreted and accumulates preferentially in bone, from which it is slowly remobilized into the bloodstream over years to decades, sustaining chronic systemic exposure long after the original source has been removed [24, 18].

The global health burden attributable to lead remains substantial. The World Health Organization estimates that lead exposure contributes to millions of deaths and tens of millions of disability-adjusted life years annually, with cardiovascular and renal pathways representing major contributors to this burden [6]. Epidemiological modelling of the Global Burden of Disease further indicates that lead-attributable mortality and morbidity,

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while declining in high-income regions, remain disproportionately concentrated in low- and middle-income countries with weaker regulatory control of industrial and recycling activities [15].

Mechanistically, lead toxicity is driven substantially by its capacity to mimic essential divalent cations such as calcium and zinc, displacing them from enzymes, structural proteins, and signaling molecules [3]. This ionic mimicry, together with direct interference with mitochondrial electron transport, promotes excessive generation of reactive oxygen species (ROS) that overwhelm endogenous antioxidant defenses, resulting in lipid peroxidation, protein oxidation, and DNA damage [11, 16]. In the kidney, this oxidative burden is compounded by the organ's intrinsically high blood flow, metabolic activity, and central role in the filtration, reabsorption, and excretion of circulating solutes, all of which render the nephron particularly susceptible to xenobiotic injury [2, 12, 23].

Clinically, renal injury is most commonly inferred from circulating biomarkers such as urea, creatinine, and uric acid. Urea is the terminal product of hepatic amino-acid catabolism and is filtered and partially reabsorbed along the nephron, such that its serum concentration reflects both protein metabolism and glomerular handling [13]. Creatinine, by contrast, is generated at a comparatively constant rate from muscle creatine and is freely filtered with minimal tubular reabsorption, making it a more specific surrogate of glomerular filtration rate [9]. Uric acid, the end product of purine metabolism, is filtered and undergoes substantial tubular reabsorption and secretion; accumulating evidence links impaired renal uric acid handling to early nephron stress and to the subsequent progression of chronic kidney disease, independent of more conventional indices [20, 21].

A substantial experimental literature has documented that oral lead acetate administration produces dose- and duration-dependent elevations in these renal biomarkers in rodent models, frequently accompanied by histological evidence of glomerular and tubular injury [5, 4, 25, 17]. Comparable hepatorenal injury has also been reported following exposure to other nephrotoxic heavy metals such as cadmium, underscoring shared oxidative and inflammatory pathways across this class of toxicants [29, 30, 19]. At the tissue level, recent work has emphasised the contribution of pro-inflammatory cytokine activation and, more recently, pyroptotic cell death pathways to lead-induced renal pathology, extending earlier descriptions of glomerular shrinkage, tubular dilation, and interstitial vascular congestion [8, 1].

Despite this body of evidence, relatively few studies combine a graded, multi-dose design with simultaneous biochemical and histopathological assessment over a defined subacute exposure window, limiting the precision with which dose-response relationships can be characterised for risk-assessment purposes [7, 27]. Environmental routes of exposure—including airborne particulates and contaminated dust—further complicate human risk estimation, reinforcing the value of controlled animal models in isolating dose-dependent renal effects [28]. The present study was therefore designed to evaluate, in a single cohesive experiment, the effects of three graded oral doses of lead acetate (100, 200, and 400 mg/kg body weight) administered for 21 days on serum urea, creatinine, and uric acid, together with the corresponding histoarchitectural changes in the kidneys of adult male Wistar rats.

MATERIALS AND METHODS

Study Design and Animals

This study employed an experimental, parallel-group, controlled in vivo design to evaluate the dose-dependent renal toxicity of lead acetate. A total of twenty (20) adult male Wistar rats, with an initial body weight range of 150–200 g, were housed in standard polypropylene cages under controlled environmental conditions (temperature 22 ± 2°C; 12-hour light/dark cycle) with ad libitum access to a standard laboratory diet and water. Following a one-week acclimatisation period, the rats were randomly allocated into four experimental groups of five animals each (n = 5):

- Group 1 (Control; n = 5): received distilled water orally.
- Group 2 (Lead-100; n = 5): received lead acetate at 100 mg/kg body weight orally.
- Group 3 (Lead-200; n = 5): received lead acetate at 200 mg/kg body weight orally.
- Group 4 (Lead-400; n = 5): received lead acetate at 400 mg/kg body weight orally.

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All doses were administered once daily by oral gavage for 21 consecutive days. The dose range was selected to span low, intermediate, and high sub-lethal exposures consistent with previous subacute lead acetate toxicity paradigms in rodents [25, 17].

Sample Collection and Biochemical Analysis

At the end of the 21-day exposure period, blood samples were collected and allowed to clot, and serum was separated by centrifugation for determination of urea, creatinine, and uric acid concentrations using standard diagnostic assay procedures. All biochemical values are expressed in mg/dl.

Histopathological Processing

Kidneys were harvested, rinsed in normal saline, and fixed for histological processing. Tissue sections were dehydrated through graded alcohols, embedded in paraffin wax, sectioned, and stained with haematoxylin and eosin (H&E) for light-microscopic examination at ×100 magnification, consistent with standard renal histopathological assessment protocols (Moneim et al., 2023). Sections were evaluated for glomerular morphology (corpuscle integrity, Bowman's space), tubular architecture (epithelial lining, luminal dilation), and interstitial changes (congestion, inflammatory infiltrate, haemorrhage).

Statistical Analysis

Experimental data are presented as mean ± standard error of the mean (SEM). Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL). One-way analysis of variance (ANOVA) was used to compare variables among groups, with post hoc comparisons performed using Duncan's Multiple Range Test. Differences between means were considered statistically significant at $p < 0.05$.

RESULTS

Effect of Lead Acetate on Serum Renal Biomarkers

Oral administration of lead acetate produced dose-dependent alterations in serum biochemical markers of renal function (Table 1). Serum urea concentrations were marginally lower than control in the 100 mg/kg (73.38 mg/dl) and 200 mg/kg (68.83 mg/dl) groups, but rose above control values in the 400 mg/kg group (80.42 mg/dl versus 74.98 mg/dl in control), a pattern consistent with declining glomerular filtration capacity specifically at the highest dose tested. Serum creatinine followed a similar trajectory, remaining close to control in the 100 mg/kg (0.97 mg/dl) and 200 mg/kg (1.03 mg/dl) groups before increasing to its highest value in the 400 mg/kg group (1.13 mg/dl versus 1.00 mg/dl in control).

Serum uric acid, by contrast, was elevated relative to control across the lower and upper dose groups: concentrations rose from 7.76 mg/dl in control to 8.82 mg/dl in the 100 mg/kg group and 8.88 mg/dl in the 400 mg/kg group, both representing statistically significant elevations ($p < 0.05$), while the 200 mg/kg group showed a smaller, non-significant increase (8.12 mg/dl). This pattern indicates that uric acid handling was disturbed even at the lowest dose of lead acetate tested, ahead of any significant change in urea or creatinine, suggesting that uric acid may serve as a more sensitive early indicator of lead-induced renal stress than the conventional excretory markers in this model.

Table 1. Serum biochemical markers of renal function across experimental groups (mg/dl).

Parameter	Control	100 mg/kg	200 mg/kg	400 mg/kg
Urea (mg/dl)	74.98	73.38	68.83	80.42
Creatinine (mg/dl)	1.00	0.97	1.03	1.13
Uric Acid (mg/dl)	7.76	8.82	8.12	8.88

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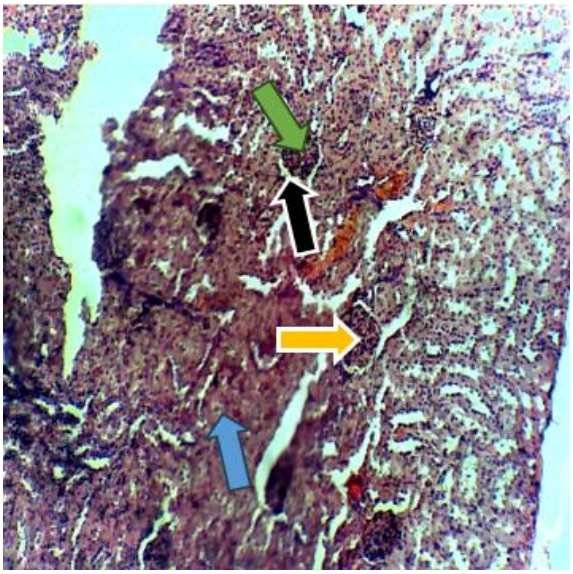
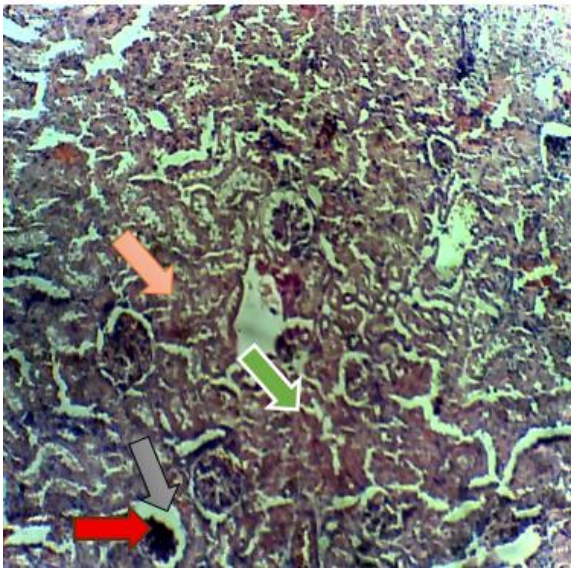
Histopathological Findings

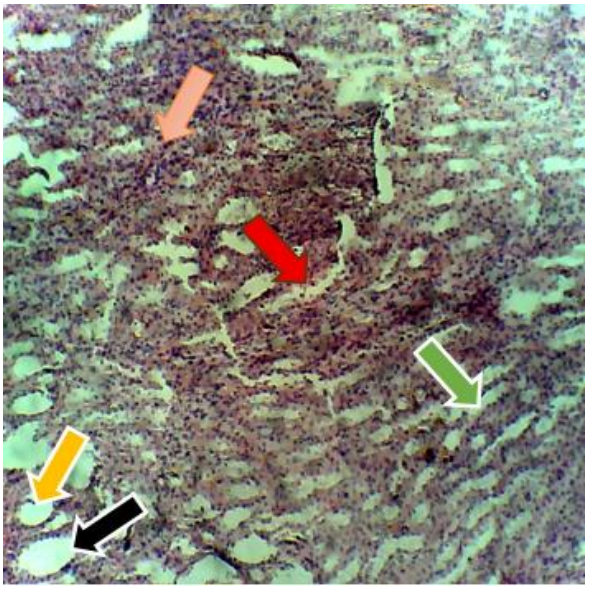
Figure 1. Photomicrographs of H&E-stained kidney sections (×100) across experimental groups.



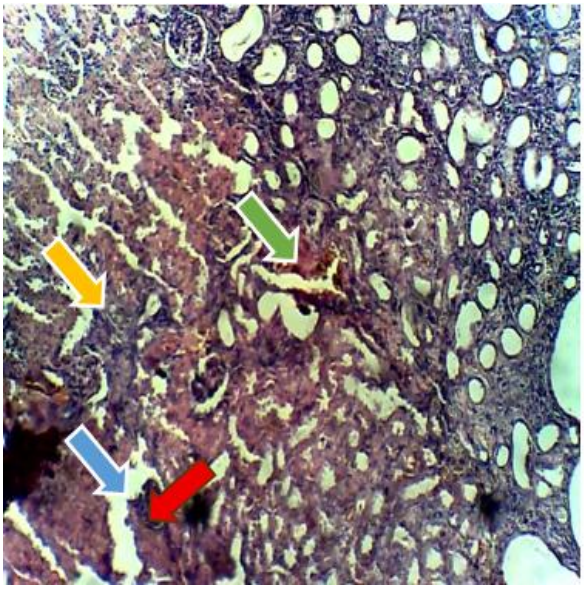
(A) Control



(B) 100 mg/kg lead acetate



(C) 200 mg/kg lead acetate



(D) 400 mg/kg lead acetate

Photomicrographs of H&E-stained kidney sections (×100) revealed a clear dose-dependent gradient of structural injury across the four experimental groups (Figure 1).

Control group (Figure 1A): Kidney sections from control animals displayed normal renal architecture, with well-defined renal corpuscles, intact glomerular tufts, a normal Bowman's space, and densely packed renal tubules with a preserved epithelial lining within minimal interstitial spaces.

Lead-100 group (Figure 1B): Sections from animals receiving 100 mg/kg lead acetate showed mild renal alterations, characterised by slightly shrunken glomeruli, mildly widened Bowman's space, early tubular dilatation, and mild epithelial cell degeneration accompanied by slight vascular congestion.

Lead-200 group (Figure 1C): Sections from animals receiving 200 mg/kg lead acetate exhibited moderate renal damage, including distorted and partially collapsed glomeruli, widened Bowman's space, marked tubular dilatation with epithelial degeneration, luminal irregularities with cellular desquamation, intense inflammatory infiltration, and pronounced vascular congestion with widened interstitial spaces.

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Lead-400 group (Figure 1D): Sections from animals receiving 400 mg/kg lead acetate showed the most severe histological changes, with severely distorted and collapsed glomeruli, markedly widened Bowman's space, severe tubular dilation with extensive epithelial degeneration, severe vascular congestion and haemorrhage, and extensive interstitial widening with inflammatory infiltrate.

Collectively, these histological findings paralleled the biochemical results, with the severity of structural injury increasing progressively from the control through the 100, 200, and 400 mg/kg groups.

DISCUSSION

The present findings demonstrate that subacute oral exposure to lead acetate produces dose-dependent biochemical and histological evidence of nephrotoxicity in adult male Wistar rats, consistent with a substantial body of prior rodent literature describing lead as a potent renal toxicant [5, 25, 4]. The numerical rise in serum urea and creatinine at the highest dose (400 mg/kg) mirrors the pattern reported in comparable Wistar rat models, in which elevations of these excretory markers have been interpreted as evidence of reduced glomerular filtration capacity following high-dose lead exposure [5, 9]. Because creatinine is generated at a relatively constant rate and undergoes minimal tubular reabsorption, its preferential elevation at the highest dose in the present study is consistent with prior observations that creatinine is a more dose-responsive indicator of renal compromise than urea, whose serum concentration can be influenced by dietary protein intake, hepatic urea-cycle activity, and variable tubular reabsorption along the nephron [13, 12].

A notable feature of the present dataset is the comparatively modest deviation from control observed in the 200 mg/kg group relative to both the 100 mg/kg and 400 mg/kg groups for urea and creatinine. Non-monotonic biochemical responses of this kind have occasionally been reported in sub-acute heavy-metal exposure paradigms and may reflect a combination of inter-individual variability inherent to small group sizes, transient compensatory adaptation of renal tubular handling at intermediate exposure, or induction of metal-binding and antioxidant defense proteins that partially offset biochemical derangement before being overwhelmed at higher doses [14, 18]. Importantly, this biochemical plateau at 200 mg/kg was not mirrored histologically, where structural injury increased progressively with dose; this dissociation reinforces the established principle that serum biomarkers alone may underestimate the extent of underlying renal injury, and that histopathological correlation remains essential for accurate toxicological interpretation [22, 8].

The significant elevation of serum uric acid at both the lowest (100 mg/kg) and highest (400 mg/kg) doses, ahead of comparable changes in urea or creatinine, is consistent with a growing body of evidence implicating disturbed renal uric acid handling as an early and sensitive marker of nephron stress. Hyperuricemia has been mechanistically linked to impaired tubular secretion and to lead-induced disruption of urate transport, and has been shown in both occupational and experimental settings to precede more overt deterioration of glomerular filtration [20, 21]. The present results, in which uric acid rose significantly even at the lowest dose tested while urea and creatinine remained comparatively stable, support the proposition that uric acid may offer added sensitivity for the early biochemical detection of lead-induced renal stress, a finding with potential relevance for biomonitoring strategies in lead-exposed populations.

The histopathological gradient observed across the four groups—from preserved architecture in controls, through mild glomerular and tubular change at 100 mg/kg, to moderate inflammatory and vascular injury at 200 mg/kg, and severe glomerular collapse with haemorrhage at 400 mg/kg—is consistent with the oxidative and inflammatory mechanisms increasingly implicated in lead nephrotoxicity. Lead-induced generation of reactive oxygen species promotes lipid peroxidation of tubular and glomerular cell membranes, activates pro-inflammatory cytokine cascades, and, at higher exposure intensities, engages apoptotic and pyroptotic cell death pathways that manifest histologically as cellular desquamation, leukocyte infiltration, and vascular congestion [11, 2, 8]. The progressive widening of Bowman's space and glomerular collapse observed at the higher doses in the present study mirror similar descriptions in other lead acetate-exposed Wistar rat models [3, 4], as well as in models of cadmium-induced hepatorenal injury that share overlapping oxidative pathways with lead [29, 30, 19].

These findings carry broader public health relevance. Lead remains a major contributor to the global burden of

kidney disease, with both occupational and environmental exposure routes—including contaminated dust, informal recycling activities, and ambient air pollution—implicated in chronic renal impairment in human populations [6, 15, 26, 28]. The dose-dependent biochemical and structural injury demonstrated here reinforces calls for stricter environmental and occupational exposure limits, alongside renal biomonitoring programmes that incorporate sensitive markers such as uric acid rather than relying solely on conventional urea and creatinine measurement [27, 24]. The continued exploration of nephroprotective agents—ranging from plant-derived antioxidants to monoterpenes and probiotics—in experimental lead acetate models further underscores the translational value of well-characterised dose-response data of the kind generated in this study [17, 4].

Several limitations should be acknowledged. The relatively small group size (n = 5) limits statistical power to detect modest inter-group differences and may have contributed to the non-monotonic pattern observed for urea and creatinine at the intermediate dose. The 21-day exposure window, while sufficient to demonstrate clear dose-dependent injury, does not capture the consequences of chronic, lower-level exposure more representative of typical human environmental contact, nor does it include a recovery cohort to evaluate the reversibility of observed changes. Only male rats were studied, precluding assessment of potential sex-related differences in susceptibility, and histological evaluation was limited to H&E staining without additional special stains or quantitative morphometric scoring. Future studies incorporating extended exposure durations, recovery groups, sex-disaggregated cohorts, additional injury biomarkers, and candidate nephroprotective interventions would further strengthen the translational relevance of these findings [7].

CONCLUSION

This study demonstrates that 21-day oral administration of lead acetate produces dose-dependent nephrotoxicity in adult male Wistar rats, evidenced by both serum biochemical alterations and progressive histopathological injury. Serum uric acid emerged as a particularly sensitive early biomarker, rising significantly even at the lowest dose tested, while urea and creatinine elevations were most apparent at the highest dose, paralleling a clear histological gradient from preserved architecture in controls to severe glomerular collapse, haemorrhage, and inflammatory infiltration at the highest exposure level. These findings reaffirm the kidney as a primary target of lead toxicity and support the integration of multiple biomarkers, alongside histopathological assessment, in both experimental and clinical evaluation of lead-induced renal injury. Given the continued global burden of environmental and occupational lead exposure, these results underscore the importance of exposure mitigation, renal biomonitoring, and continued investigation of protective therapeutic strategies.

DECLARATIONS: All animal procedures were conducted in accordance with institutional and international guidelines for the care and use of laboratory animals, following review and approval by Nile University of Nigeria Abuja Animal Care and Use Committee/Ethics Committee.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

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