Original Article

The Possible Protective Effect of L-Carnitine against Gentamicin-Induced Acute Renal Injury in Rats

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Abstract

Background: Several studies concerned the role of free radicals in gentamicin-induced kidney injury, where reactive oxygen species (ROS) directly damage lipids, proteins, and DNA, which are the basic structures of cell components, including membrane lipid peroxidation during oxidative stress. **Objectives:** The study aimed to investigate the potential protective effects of L-carnitine against gentamicin-induced nephrotoxicity in rats. **Materials and Methods:** Twenty-four male rats (*Rattus norvegicus*) were classified into four groups: Group-1: the animals received a single daily dose of normal saline solution (N.S.) for 2 weeks and served as the control; Group-2: Animals in this group were injected intra-peritoneally with a daily dose of gentamicin (60 mg/kg) for 2 weeks to induce renal injury. Group-3: Animals in this group received a daily dose of L-carnitine (60 mg/kg) via intra-peritoneal injection for 2 weeks. Group-4: Animals in this group were co-administered with a daily dose of gentamicin (60 mg/kg) via intra-peritoneal injection and L-carnitine daily dose intra-peritoneal injection (60 mg/ kg) for 2 weeks. **Results:** Gentamicin (60 mg/kg) for 2 weeks revealed a significant increase in the serum levels of urea and creatinine in comparison to the control group. Also, the induction group showed a significant decrease in the serum levels of glutathione (GSH) and superoxide dismutase compared to the control group. While the level of kidney injury molecule-1 (KIM) was decreased in the gentamycin group in comparison with the control group, and the L-carnitine group showed a significant improvement in the levels of urea, creatinine, and GSH compared to the gentamycin group. In addition, the level of KIM was significantly reduced in the L-carnitine–treated group in comparison with the induction group. Furthermore, the L-carnitine showed amelioration in histopathological changes of renal tissues in comparison to the gentamycin-treated group. **Conclusion:** The results of this study indicate that L-carnitine has a protective effect against gentamicin-induced renal injury, which is nephrotoxicity caused by gentamicin.

Keywords: Acute kidney injury (AKI), gentamicin, gentamicin nephrotoxicity, L-carnitine

Introduction

The nephrons are the basic functional units of the kidneys, which are composed of the vascular elements, the glomerulus, and the tubular elements, which contribute to their primary role.

First, the regulation of homeostatic equilibrium of body fluids is done via filtering and secretion of metabolites such as urea and minerals from the blood and excretion of wastes as urine.[1] Second, the kidneys also play significant roles in the regulation of blood pressure and carbohydrate metabolism because they control the plasma concentrations of O_2, Na^+, K^+, and H^+ ions and other compounds like amino acids, creatinine, bicarbonate, and glucose.[2]

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Finally, the kidneys are the major site for the synthesis and release of hormones such as renin, erythropoietin, 1,25-dihydroxy vitamin D3; vasoactive prostaglandins (PGF-2; PGE-1) and kinins influence systemic metabolic functions.[3]

All parts of the nephron are potentially exposed to the harmful effects of toxicants.However, most toxicants favorably disturb specific parts of the kidney; nephrotoxicity caused by most drugs has been induced by different pathogenic mechanisms, including altered intra-glomerular hemodynamics, tubular cell toxicity and tubular obstruction, inhibition of oxidative phosphorylation, disturbance of Ca2+ homeostasis, and thrombotic micro-angiopathy.[4,5]

The standard procedures for evaluating the renal function involve the measurement of the serum level of urea and serum level of creatinine; these parameters are considered nonspecific and insensitive, especially in the assessment of acute renal injury. It is essential to distinguish that alterations in the serum levels of BUN and creatinine concentrations predominantly imitate functional variations in the renal filtration capacity and are not considered accurate injury biomarkers. Thus, biomarkers such as kidney injury molecule-1 (KIM-1 have been discovered to play an important role in the diagnosis of early acute kidney injury (AKI) .[6,7] Additionally, other biomarkers are recently considered in the evaluation and diagnosis of AKI like neutrophil gelatinase-associated lipocalin, interleukin-18 (IL-18), and tissue inhibitor of metalloproteinase 2.[8,9]

KIM-1 once detected is considered a sensitive and specific urinary biomarker of kidney injury in the pathophysiology of kidney injury,[10] which has been revealed in most preclinical studies to be more subtle than BUN and creatinine as a biomarker for injury. In fact, the Food and Drug Administration now consider KIM-1 in the assessment of kidney injury as part of their particular drug evaluation processes for newly discovered drugs.[11]

Gentamicin is an aminoglycoside antibiotic clinically used in the treatment of Gram-negative bacterial infections alone or in cooperation with beta-lactam antibiotics. Gentamicin-induced nephrotoxicity via destruction of cellular constituents, lysosomal swelling,and mitochondrial damage that cause tissue necrosis lead to functional alterations obvious by proteinuria and increased serum levels of urea and creatinine, which lead to acute kidney damage.[12]

Gentamicin produces nephrotoxicityin the kidney cortex, mainly in proximal tubules by accumulation in lysosomes.[13] There are other pathways through which gentamicin induces nephrotoxicity, which involves reduction of renal blood flow, oxidative stress via lipid peroxidation, generation of nitric oxide (NO), the nuclear factor-B pathway, inflammation, and apoptosis.[14]

Several studies focused on the role of free radicals in gentamicin-induced kidney injury, where reactive oxygen species (ROS) directly damage lipids, proteins, and DNA, which are the basic structures of cell components, and also membrane lipid peroxidation during oxidative stress.[15]

It is shown that gentamicin causes simultaneous mesangial proliferation and apoptosis in rats kidneys via production of ROS by renal cortical mitochondria.[16] ROS abolish the glomerular basement membrane, interrupt with renal tubular function, and destroy the collagen and other matrix proteins.[17] Finally, gentamicin reduces the activity of reno-protective enzymes such as superoxide dismutase (SOD), catalase, glutathione (GSH) peroxidase, and reduced GSH.[18]

L-carnitine is an L-lysine derivative, an endogenous compound; its main physiological function in the body is enabling or transportation of fatty acids into the mitochondria to enter the B-oxidation cycle.[19] The protective effects of L-carnitine on various tissues have been proved in various models involving cisplatin-induced oxidative stress in the kidney and small intestine and gentamicin-induced ischemic–reperfusion kidney injury.[19]

L-carnitine facilitates the transfer of long-chain fatty acids into the mitochondria of the other tissues, where they enter B-oxidation.[20] Through this mechanism, L-carnitine greatly effects fatty acid oxidation in these tissues and maintains low pools of fatty acid (acyl)-coenzyme A compounds, which are potentially toxic.[21] Other mechanisms of L-carnitine may involve stabilization of erythrocyte cellular membranes;[22] increased production of ATP tissues, probably by oxidation of fatty acid;[23] and finally, inhibition of production of free radical like ROS.[24]

This study was designed to detect the probable protective effects of Lcarnitine against gentamicin-induced nephrotoxicity in rats.

Materials and Methods

Experimental animals

Twenty-four male rats (*Rattus norvegicus*) obtained from Faculty of Pharmacy, University of Kerbala, were used in the present study. Their weight range was between 100 gm. Rats were provided with water. The animals were housed in plastic cages in the College of Pharmacy/University of Kerbala under suitable environment conditions at temperature 23 ± 2°C. Rat chow and water were offered daily, and they were kept for 2 weeks before the beginning of the experiment for acclimation.

Experimental design

Twenty-four male rats weighing 250–300 g were divided into four groups involving six animals in each group as follows:

Group-1: Rats received a single daily dose of normal saline solution (NS) via intra-peritoneal injection (IP) for 2 weeks and considered the control group.

Group-2: Rats in this group received an intra-peritoneal daily dose of gentamicin (60mg/kg) for 2 weeks to induce renal injury.

Group-3: Rats in this group received L-carnitine daily dose (60 mg/kg) as an intra-peritoneal (IP) injection for 2 weeks.

Group-4: Rats in this group were co-administrated with a daily dose of gentamicin (60 mg/kg) as an intra-peritoneal injection and L-carnitine daily dose intra-peritoneal injection (60 mg/ kg) for 2 weeks.

Drugs used in the experiment

Gentamicin ampoule (80 mg/2 mL-Megental) was given to the rats in a dose of 60 mg/kg as an intra-peritoneal daily dose for 2 weeks.

L-carnitine ampule (1gm/5 mL – lecithin) was given to the rats in a dose of 60 mg/kg as an intra-peritoneal daily dose for 2 weeks.

Biochemical assay

After 2 weeks of treatment in the morning of day 15, after the animals were anesthetized with chloroform, the blood was obtained directly from the heart of each animal, and then the rats were killed, the collected blood was put in a plan gel tube and left to stand for 30 min. After centrifugation of the blood sample at 3000 ×g for 10 min, the serum was obtained and then estimation of urea by ELISA assay was performed according to the instructions in the kit of Biomerieux company,[17] and also estimation of creatinine by ELISA assay following the procedure provided by the Syrbio company.[18]

Histological examinations

Both kidneys were removed from each rat at the end of the experiment and are reserved in 10% formalin solution and then embedded in paraffin and prepared as 5-mm-thick sections stained with hematoxylin and eosin (H and E); here, now the histopathological assessment was focused on morphological changes in the renal tissue caused by gentamicin, which mainly involved the proximal tubules in which other renal structures do not show major histological alterations.[25]

Statistical analysis

The data of this study are expressed as mean ± standard error of mean. Statistical analysis had been done by using independent *t* test. Significant difference was set at $P < 0.05$.

Results

1. Effects of L-carnitine 60 mg/kg/day for 2-week treatment on the serum levels of urea and creatinine against gentamicin (60 mg/kg/day)-induced nephrotoxicity in rats:

Data of all groups are expressed as (Mean±SE) as shown in Table 1, In group-II, rats received an IP daily dose of gentamicin (60 mg/kg) for 2 weeks, which revealed a significant increase in the serum levels of urea and creatinine ([59.01 ± 2.59], [3.15 ± 0.46]), respectively, compared to the control group (urea= 18 ± 0.89); (creatinine=0.16 ± 0.04) ($P < 0.05$), [Figures 1 and 2].

In group-III, treatment of rats with an IP daily dose of L-carnitine (60 mg/kg) for 2 weeks showed a significant reduction in the serum levels of urea and creatinine ([24.5 ± 1.43], [0.33 ± 0.94]), respectively, compared to that observed in group-II ($P < 0.05$); however, the results revealed a nonsignificant difference compared to the control group ($P > 0.05$), [Figures 1 and 2].While rats treated with an IP daily dose of L-carnitine injection (60 mg/kg) for 2 weeks prior to and during IP gentamicin administration (60 mg/kg) in group-IV created a significant

Table 1: Effects of L-carnitine treatment on the serum levels of (urea, creatinine, GSH, SOD, and KIM-1) in rats compared to control and gentamicin-treated groups (values with non-identical characters (a,c) are considered significantly different ($P < 0.05$)

Groups ($N = 6$/group)	Group-I	Group-II	Group-III	Group-IV
Mean urea level mg/dl	18 ± 0.89	59.01 ± 2.59 A	24.5 ± 1.43 NS, b	38.33 ± 2.81 NS, b
Mean creatinine level mg/dl	0.16 ± 0.04	3.15 ± 0.46 A	0.33 ± 0.94 NS, b	1.36 ± 0.48 NS, b
Mean GSH level mg/dl	7.07 ± 0.27	4.92 ± 0.31 A	10.62 ± 0.47 NS, b	9.96 ± 0.50 NS, b
Mean SOD level mg/dl	23.32 ± 1.38	20.98 ± 0.81 A	42.50 ± 1.06 NS, b	38.62 ± 1.68 NS, b
Mean KIM-1 level mg/dl	102.61 ± 1.70	353.57 ± 26.8 A	111.55 ± 1.33 NS, b	169.24 ± 7.77 NS, b

Data are presented as mean ± SEM, N = number of animals per group, Group-I: control group, Group-II: gentamicin (60 mg/kg/day), Group-III: L-carnitine (60 mg/kg/day), Group-IV: L-carnitine (60 mg/kg/day) + gentamicin (60mg/kg/day), a:$P < 0.05$ significant in compared to the control group, b: Significant to gentamicin (60 mg/kg/day), NS: Non-significant to the control group

reduction in the serum levels of urea and creatinine ([38.33 ± 2.81], [1.36 ± 0.48]), respectively, compared to that observed in group-II ($P < 0.05$), but showed a nonsignificant difference compared to the control group ($P > 0.05$) [Figures 1 and 2].

2. Effects of L-carnitine 60 mg/kg/day for 2-week treatment on the serum levels of GSH and SOD against gentamicin (60 mg/kg/day)-induced nephrotoxicity in rats:

In Group-II, rats receiving an IP daily dose of gentamicin (60 mg/kg) for 2 weeks revealed a significant decrease in the serum levels of GSH and SOD ([4.92 ± 0.31], [20.98 ± 0.81]), respectively, compared to the control group (GSH=7.07 ± 0.27), (SOD=23.32 ± 1.38) ($P < 0.05$); [Figures 3 and 4]. In group-III, treatment of rats with an IP daily dose of L-carnitine (60 mg/kg) for 2 weeks created a significant increase in the serum levels of GSH and SOD ([10.62 ± 0.47], [42.50 ± 1.06]), respectively, compared to that observed in Group-II ($P < 0.05$); however, the results revealed a nonsignificant difference compared to the control group ($P > 0.05$) [Figures 3 and 4]. While rats treated with an IP daily dose of L-carnitine injection (60 mg/kg) for 2 weeks prior to and during IP gentamicin administration (60 mg/kg) in group-IV created a significant increase in the serum levels of GSH and SOD [(9.96 ± 0.5), (38.62 ± 1.68)], respectively, compared to that observed in group-II ($P < 0.05$), but showed a non-significant difference compared to the control group ($P > 0.05$) [Figures 3 and 4].

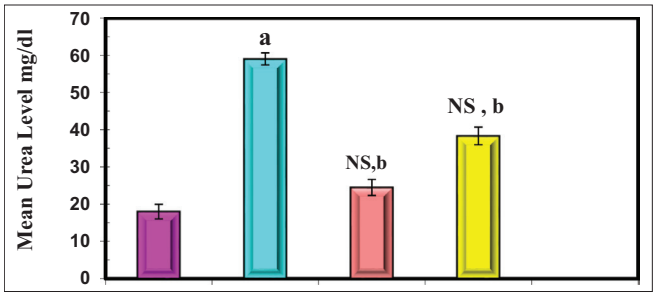

Figure 1: Effects of L-carnitine treatment on the serum level of urea in rats compared to control and gentamicin-treated groups values with non-identical superscripts (a and b) are considered significantly different ($P < 0.05$)

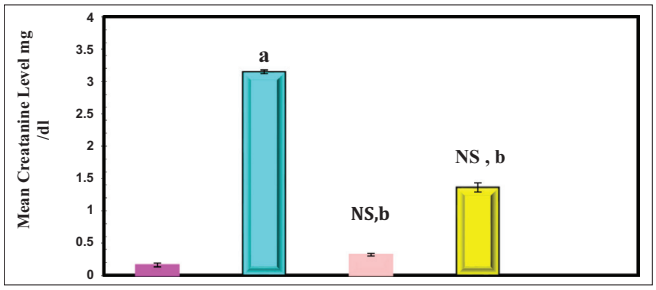

Figure 2: Effects of L-carnitine treatment on the serum level of creatinine in rats compared to control and gentamicin-treated groups values with non-identical superscripts (a and b) are considered significantly different ($P < 0.05$)

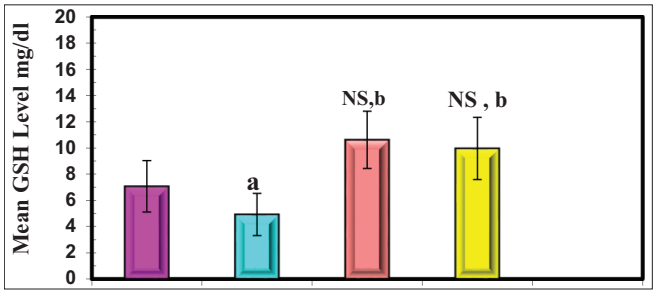

Figure 3: Effects of L-carnitine treatment on the serum level of GSH in rats compared to control and gentamicin-treated group values with non-identical superscripts (a and b) are considered significantly different ($P < 0.05$)

Effects of L-carnitine 60 mg/kg/day for 2-week treatment on the serum levels of kidney injury molecule-1 (KIM-1) against gentamicin (60 mg/kg/day)-induced nephrotoxicity in rats:

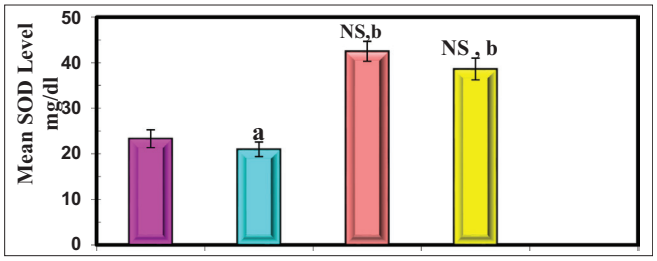

Figure 4: Effects of L-carnitine treatment on the serum level of SOD in rats compared to control and gentamicin treated groups values with non-identical superscripts (a and b) are considered significantly different ($P < 0.05$)

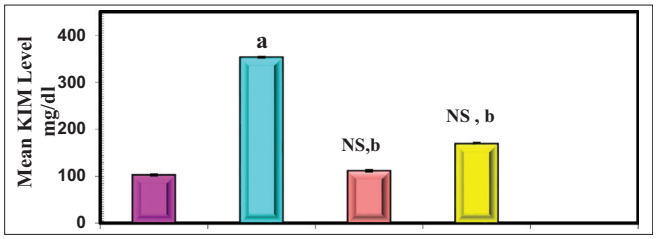

Figure 5: Effects of L-carnitine treatment on the serum level of KIM-1 in rats compared to control and gentamicin-treated groups values with non-identical superscripts (a and b) are considered significantly different ($P < 0.05$).

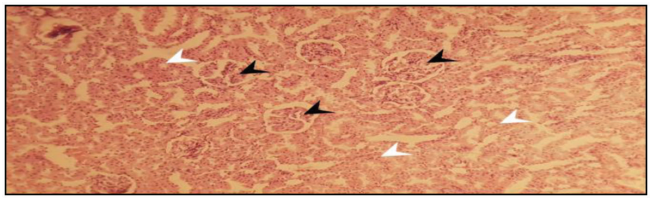

Figure 6: Kidney of the negative control group shows normal glomeruli (black arrowhead) normal renal tubules (white arrow head) H and E 125×

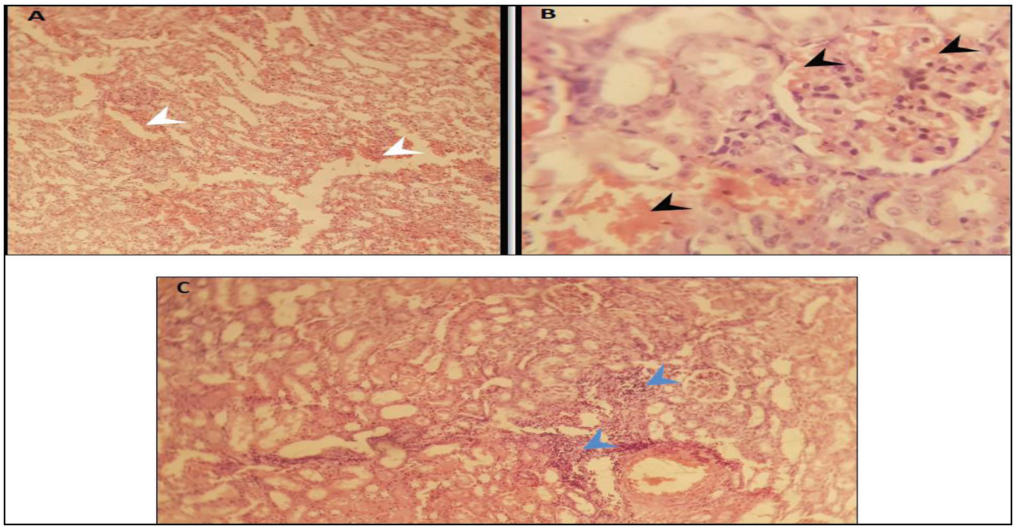

Figure 7: Kidney of the gentamicin-treated group exhibits glomerular congestion (black arrowhead), interstitial hemorrhage (white arrowhead), and inflammation (blue arrow head) H and E (A and C) 125 × (B) 500×

In group-II, rats that received an IP daily dose of gentamicin (60 mg/kg) for 2 weeks showed a significant increase in the serum levels of (KIM-1 = 353.57 ± 26.8) compared to the control group (KIM-1 = 102.61 ± 1.7) ($P < 0.05$) [Figure 5]. In group-III, treatment of rats with an IP daily dose of L-carnitine (60mg/kg) for 2 weeks created a significant reduction in the serum levels of (KIM-1 = 111.55 ± 1.33) compared to that observed in group-II ($P < 0.05$); however, the results showed a nonsignificant difference compared to the control group ($P > 0.05$) [Figure 5]. Rats treated with an IP daily dose of L-carnitine injection (60 mg/kg) for 2 weeks prior to and during IP gentamicin administration (60 mg/kg) in Group-IV revealed a significant decrease in the serum levels of (KIM-1 = 169.24 ± 7.77) compared to that observed in Group-II ($P < 0.05$), but showed a nonsignificant difference compared to the control group ($P > 0.05$) [Figure 5].

Results of Histopathological Examination of the Kidney

Histopathological evaluation revealed in group-II that rats treated with gentamicin for 14 days showed glomerular congestion, interstitial hemorrhage, and inflammation compared to the control group, which exhibited normal glomeruli with normal renal tubules [Figures 6 and 7]. In Group-III, treatment of rats with L-carnitine for 14 days revealed that both glomeruli and renal tubules are normal compared to what was observed in group II [Figure 8], whereas rats treated with L-carnitine (60 mg/kg/day) injection intra-peritoneally for 14 days prior to and during intraperitoneal administration of gentamicin (60 mg/kg/day) in group-IV displayed a normal glomerulus with normal renal tubules compared to that observed in group II [Figure 9].

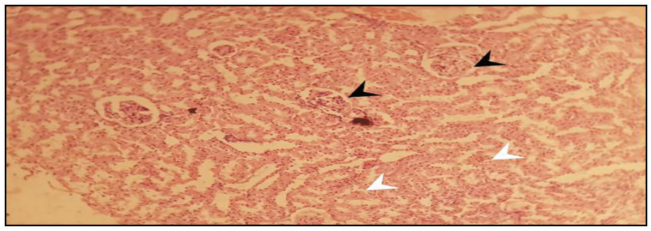

Figure 8: Kidney of the L-carnitine–treated group shows normal glomeruli (black arrowhead) and normal renal tubules (white arrowhead) H and E 125×

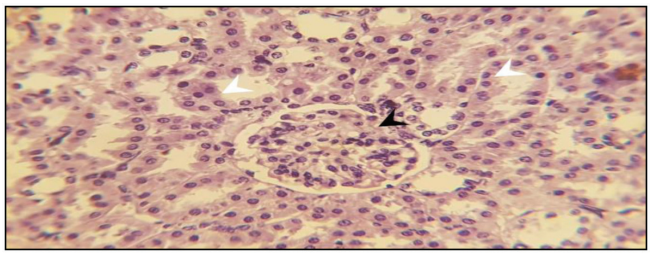

Figure 9: Kidney of gentamicin with the L-carnitine treated group shows a normal glomerulus (black arrowhead) normal renal tubules (white arrowhead) H and E 500×

Discussion

Primary diagnosis of AKI plays an important role in its treatment and prognosis. AKI commonly distinguished by elevated serum levels of urea, creatinine, or reduced urine output. So there is a critical need to find a more effective diagnostic measurement for AKI; new biomarkers are considered to have a potential role in the diagnosis of AKI, one of which is the serum KIM-1.

Gentamicin induced renal damage in rats at a daily dose of 60 mg/kg, causing a mild form of renal toxicity, whereas a high dose was employed in a previous study

to produce severe renal damage; the induction period of 2 weeks has been shown to induce acute kidney damage with sufficiency.[26]

The L-carnitine daily dose of 60 mg/kg was selected to observe whether this dose could protect against gentamicin-induced nephrotoxicity; also, L-carnitine injections were initiated 4 days prior to initiation of gentamicin in order to offer some assurance that if L-carnitine was not revealed to have protective effects, it could not be attributed to insufficient levels of time when gentamicin induced renal damage without adequate levels of L-carnitine.[27]

In the present study, in group II, the injections of a daily dose of gentamicin 60 mg/kg IP induced renal injury, showing a significant increase in the serum levels of BUN, Cr, and KIM-1 and significant reduction in serum levels of GSH and SOD at day 14. So the basic explanation for these results is that they are caused by reduction of the glomerular filtration rate (GFR), which is a decrease in the renal capacity to filter creatinine and waste products.[28,29] Other explanations for these results are renal tubular damage, compromised reabsorptive capability of tubular protein, or impaired protein filtration through the glomerular barriers due to high levels of urea and uric acid.[30]

Gentamicin induces oxidative stress via ROS, which contributed in nephrotoxicity. ROS play a role through different mechanisms leading to reduced GFR, which ended with tubular necrosis;[31] interaction of excessively produced ROS such as superoxide anions, hydrogen peroxide (H2O2), hydroxyl radicals ($OH^{\cdot}$), and reactive nitrogen species with other components like lipids results from peroxidation of unsaturated fatty acids in the cell membrane and denaturation of proteins resulting in cell and tissue damage.[32]

Research suggests that other mechanisms of gentamicin-induced nephrotoxicity involve the reaction of gentamicin with the structural functional unit of biological membranes.[33] That is, gentamicin reacts and binds to anionic phospholipids that alter the physical properties and functions of cell membranes via diminishing the permeability of the glycerol moiety of phosphatidylinositol,[34] reducing membrane flexibility and promoting membrane aggregation.[35]

Other studies revealed that gentamicin induced renal tissue injury via exhaustion of renal GSH, which caused lipid peroxidation; this assessment is maintained by a reduction in GSH levels and kidney antioxidant enzymes like SOD in the renal tissues.[36,37]

KIM-1 plays an essential role in kidney injury and the associated recovery processes.[38] Studies have suggested that KIM-1 is considered a sensitive and specific marker of acute kidney damage.[39] It is expressed at high levels in the kidney tissues, which is dramatically up-regulated when the renal tissues undergo ischemic injury.[40]

Also, in group-III & group-IV, the rats received a daily dose of L-carnitine (60 mg/kg); at the end of 2 weeks, the result revealed a low level in serum concentrations of urea and creatinine and KIM-1 and a higher level in serum concentrations of GSH and SOD. The mechanisms of action by which L-carnitine may ameliorate gentamicin-induced nephrotoxicity in rats are unclear, but the protecting effect of L-carnitine on renal tissue was proven to possibly be related to improvement in oxidative stress via regulation of NO and cellular respiration.[41] In the present study, L-carnitine had a protective effect on the activity of enzymes involved in the defense against oxidative damage; also, the antioxidant and free radical scavenger roles of L-carnitine shown via changes in serum GSH level and serum SOD level caused by ROS were significantly alleviated by pretreatment of L-carnitine, and these results are correlated with those of the previous study that showed evidence that L-carnitine not only has an antioxidant effect but is also a free radical scavenger.[42-44]

These events are related with other studies that also reported that L-carnitine has a distinct protective effect against renal ischemic–reperfusion injury.[44] Moreover, it is referred from a previous study that L-carnitine reduces oxidative stress in the rat renal tissues via reduction of lipid peroxidation and decreased intracellular ATP levels.[45-47]

Finally, the histological data in group-2 indicate that most rats receiving gentamicin showed glomerular congestion, interstitial hemorrhage, and inflammation in comparison with that observed in the control (group-1). However, histopathological data in [Figure 3] showed normal glomeruli with normal renal tubules, which refer to the protective role of L-carnitine against gentamicin-induced renal damage. Similarly, in group-4 that involved rats receiving a daily dose of gentamicin 60 mg/kg in combination with a daily dose of L-carnitine 60 mg/kg, the histopathological findings in [Figure 4] also showed normal glomeruli with normal renal tubules in comparison with the gentamicin induction group.

Conclusion

The results of this study indicate that L-carnitine has a protective effect against gentamicin-induced renal injury, which is nephrotoxicity caused by gentamicin.

Ethical approval

The study protocols were conducted according to the ethical approval of the Ethics Committee (15/1/2023, UE/5/20), University of Al-Ameed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Rang HP, Dale MM, Ritter JM, Flower RJ. Pharmacology: The Kidney. 6th ed. Churchil Livingstone; 2007. p. 368-384.
2. Gerard J, Lennart D. Safety science of drugs. In: Pharmaceutical toxicology: Kidney toxicity. 2nd ed. Mulder Dencker, London: Pharmaceutical Press; 2007. p. 160-169.
3. Ganong WF. Review of medical physiology. Dynamics Blood Lymph Flow 1995;30:525-41.
4. Tarloff JB, Wallace AD. Biochemical mechanisms of renal toxicity. In: Smart RC, Hodgson E, editors. Molecular and biochemical toxicology. 4th ed. Hoboken, New Jersey: John Wiley and Sons Inc.; 2008. p. 707.
5. Sharma V, Singh TG. Drug induced nephrotoxicity-A mechanistic approach. Mol Biol Rep 2023;50:6975-86.
6. Waikar SS, Bonventre JV. Biomarkers for the diagnosis of acute kidney injury. Nephron Clin Pract 2008;109:c192-7.
7. Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of acute kidney injury. Annu Rev Pharmacol Toxicol 2008;48:463-93.
8. Kashani K, Cheungpasitporn W, Ronco C. Biomarkers of acute kidney injury: The pathway from discovery to clinical adoption. Clin Chem Lab Med 2017;55:1074-89.
9. Schrezenmeier EV, *et al*. Biomarkers in acute kidney injury–pathophysiological basis and clinical performance. Acta Physiologica 2017;219:556-74.
10. Sutton TA. Alteration of microvascular permeability in acute kidney injury. Microvasc Res 2009;77:4-7.
11. Boesen K, Gøtzsche PC, Ioannidis JPA. EMA and FDA psychiatric drug trial guidelines: Assessment of guideline development and trial design recommendations. Epidemiol Psychiatr Sci 2021;30:e35.
12. Begg EJ, Barclay ML, Kirkpatrick CMJ. The therapeutic monitoring of antimicrobial agents. Br J Clin Pharmacol 2001;52:35-43.
13. Christo JS, Rodrigues AM, Mouro MG, Cenedeze MA, Simões Manuel de Jesus, Schor N, *et al*. Nitric oxide (NO) is associated with gentamicin (GENTA) nephrotoxicity and the renal function recovery after suspension of GENTA treatment in rats. Nitric Oxide 2011;24:77-83.
14. Rangan G, Wang Y, Harris D. NF-kappaB signalling in chronic kidney disease. Front Biosci 2009;14:19273289.
15. Halliwell B, Chirico S. Lipid peroxidation: Its mechanism, measurement, and significance. Am J Clin Nutr 1993;57:715S-724S; discussion 724S.
16. El Mouedden M, Laurent G, Mingeot-Leclercq MP, Tulkens PM. Gentamicin-induced apoptosis in renal cell lines and embryonic rat fibroblasts. Toxicol Sci 2000;56:229-39.
17. Parlakpinar H, *et al*. Protective effect of chelerythrine on gentamicin-induced nephrotoxicity. Cell Biochem Funct 2006;24:41-8.
18. Dam VP, Scott JL, Ross A, Kinobe RT. Inhibition of cystathionine gamma-lyase and the biosynthesis of endogenous hydrogen sulphide ameliorates gentamicin-induced nephrotoxicity. Eur J Pharmacol 2012;685:165-73.
19. Junsheng YE, *et al*. L-carnitine attenuates oxidant injury in HK-2 cells via ROS-mitochondria pathway. Regul Pept 2010;161:58-66.
20. Bremer J. Carnitine--metabolism and functions. Physiol Rev 1983;63:1420-80.
21. Sharma B, Yadav DK. L-Carnitine and chronic kidney disease: A comprehensive review on nutrition and health perspectives. J Pers Med 2023;13:298.
22. Ronca F, Palmieri L, Malengo S, Bertelli A. Effect of L-propionyl carnitine on *in-vitro* membrane alteration of sickle-cell anaemia erythrocytes. Int J Tissue React 1994;16:187-94.
23. SHUG AL. Protection from adriamycin-induced cardiomyopathy in rats. Z Kardiol 1987;76:46-52.
24. Packer L, Valenza M, Serbinova E, Starke-Reed P, Frost K, Kagan V. Free radical scavenging is involved in the protective effect of L-propionyl-carnitine against ischemia-reperfusion injury of the heart. Arch Biochem Biophys 1991;288:533-7.
25. Toubeau G, Laurent G, Carlier MB, Abid S, Maldague P, Heuson-Stiennon JA, *et al*. Tissue repair in rat kidney cortex after short treatment with aminoglycosides at low doses. A comparative biochemical and morphometric study. Lab Invest 1986;54:385-93.
26. Tulkens PM. Experimental studies on nephrotoxicity of aminoglycosides at low doses: Mechanisms and perspectives. Am J Med 1986;80:105-14.
27. Golper TA, Wolfson M, Ahmad S, Hirschberg R, Kurtin P, Katz LA, *et al*. Multicenter trial of L-carnitine in maintenance hemodialysis patients. I. Carnitine concentrations and lipid effects. Kidney Int 1990;38:904-11.
28. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 1992;38:1933-53.
29. Muhammad-Baqir BM, Hameed EN, Shareef RH, Ahmed MH. Impact of erythropoietin on anemia in end-stage renal disease patients on hemodialysis. Med J Babylon 2023;20:558-63.
30. Mueller PW, Lash LH, Price RG, Stolte H, Gelpi E, Maack T, *et al*. Urinary biomarkers to detect significant effects of environmental and occupational exposure to nephrotoxins. I. Categories of tests for detecting effects of nephrotoxins. Ren Fail 1997;19:505-21.
31. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. Kidney Int 2011;79:33-45.
32. Yaman I, Balikci E. Protective effects of Nigella sativa against gentamicin-induced nephrotoxicity in rats. Exp Toxicol Pathol 2010;62:183-90.
33. Kaloyanides GJ, Ramsammy LS. Alterations of biophysical properties of liposomes predict aminoglycoside toxicity: inhibitory effect of polyaspartic acid. In: Bach PH, Delacrey L, Gregg NJ, Wilks MF, editors. Proceedings of the Fourth International Symposium on Nephrotoxicity. New York: Marcel Dekker; 1991. p. 117-126.
34. Baliga R, Ueda N, Walker PD, Shah SV. Oxidant mechanisms in toxic acute renal failure. Drug Metab Rev 1999;31:971-97.
35. Walker PD, Barri Y, Shah SV. Oxidant mechanisms in gentamicin nephrotoxicity. Ren Fail 1999;21:433-42.
36. Manikandan R, Beulaja M, Thiagarajan R, Priyadarsini A, Saravanan R, Arumugam M. Ameliorative effects of curcumin against renal injuries mediated by inducible nitric oxide synthase and nuclear factor kappa B during gentamicin-induced toxicity in Wistar rats. Eur J Pharmacol 2011;670:578-85.
37. Aygün FO, Akçam FZ, Kaya O, Ceyhan BM, Sütçü R. Caffeic acid phenethyl ester modulates gentamicin-induced oxidative nephrotoxicity in kidney of rats. Biol Trace Elem Res 2012;145:211-6.
38. Bailly V, Zhang Z, Meier W, Cate R, Sanicola M, Bonventre JV. Shedding of kidney injury molecule-1, a putative adhesion protein involved in renal regeneration. J Biol Chem 2002;277:39739-48.
39. Bonventre JV. Kidney Injury Molecule-1 (KIM-1): A specific and sensitive biomarker of kidney injury. Scand J Clin Lab Invest 2008;68:78-83.
40. Ichimura T, Bonventre JV, Bailly V, Wei H, Hession CA, Cate RL, *et al*. Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. J Biol Chem 1998;273:4135-42.
41. Brown GC. Nitric oxide and mitochondrial respiration. Biochim Biophys Acta 1999;1411:351-69.
42. Gülçin I. Antioxidant and antiradical activities of L-carnitine. Life Sci 2006;78:803-11.
43. Ali NAM. Protection against paclitaxel-induced hyperalgesia and Allodynia by Pomegranate Seed Oil, Nucleo-CMP Forte®, and L-Carnitine. Med J Babylon 2021;18:74-9.
44. Alahmar AT, Al Jothery AHT, Al-Daami QJ, Abbas A, Al-Hassnawi ATS. The effect of coenzyme Q10 on dexamethasone-induced oxidative stress in rats testes. Med J Babylon 2023;20:130-5.
45. Ergün O, Ulman C, Kiliçalp AS, Ulman I. Carnitine as a preventive agent in experimental renal ischemia-reperfusion injury. Urol Res 2001;29:186-9.
46. Longoni B, Giovannini L, Migliori M, Bertelli AA, Bertelli A. Cyclosporine-induced lipid peroxidation and propionyl carnitine protective effect. Int J Tissue React 1999;21:7-11.
47. Mustafa MQ, Mohammed ZJ. Oxidative stress evaluation of Lambda-Cyhalothrin and antioxidant (vitamin E) on male rats. Med J Babylon 2024;21:641-5.