Zagazig University Medical Journal
www.zumj.journals.ekb.eg

July.2021 Volume 27 Issue 4
Manuscript ID ZUMJ-1904-1194 (R1)
DOI 10.21608/zumj.2019.11494.1194

ORIGINAL ARTICLE

Effect of Paracetamol administration on the Rat kidney structure: A Morphological Study

Abdelmonem Awad Hegazy, Enssaf Ahmad Abd Al Hameed, Dalia Ibrahim El-Wafaey, Omnia Ahmad Esmat Khorshed **
Human Anatomy & Embryology Departments, Faculty of Medicine-Zagazig University

Corresponding author:
Omnia Ahmad Esmat Khorshed
Demonstrator in Human Anatomy &Embryology department
Faculty of Medicine-Zagazig University

omniakhorshed@outlook.com

Submit Date 2019-04-08
Revise Date 2019-05-22
Accept Date 2019-05-28

ABSTRACT

Aims: To clarify the nephrotoxic effect of paracetamol in adult male albino rats.

Methodology: In this study, fourteen adult male albino rats were divided equally into two groups; Control group and paracetamol-treated group. Kidney specimens were processed for biochemical and histological analysis.

Results: Administration of paracetamol revealed a noticeable deterioration of both biochemical and histological changes detected in the paracetamol-treated group. The biological changes were in the form of significant increase in serum urea and creatinine levels. The histological changes markedly affected the tubular system; the proximal and distal convoluted tubules showed marked degeneration, dense nuclear staining, cytoplasmic vacuolization and partial loss of the brush borders. Most tubules were dilated, irregular and filled with hyaline casts.

Conclusion: Paracetamol made biochemical and histo-pathological changes in the rats kidneys. These findings revealed that this nephrotoxicity was associated with an increase in oxidative damage and apoptosis.

Keywords: Paracetamol, Nephrotoxicity, Albino Rats

INTRODUCTION

Paracetamol or acetaminophen (N-acetyl-p-aminophenol [APAP]), is an acylated aromatic amide, a metabolite of phenacetin, that was firstly introduced into medicine as an antipyretic/analgesic by Von Mering in 1893 and has been in use as an analgesic for home medication for over 30 years **(1).**

Though paracetamol is generally considered safe for human use at recommended doses, potentially fatal liver damages occurred when an acute overdose was used or even, in rare cases, when normal doses were taken by certain individuals. Accordingly, paracetamol overdose is one of the most common causes of drug poisoning world-wide. In the United States, the United Kingdom, Australia, and New Zealand, paracetamol is the most common cause of drug overdoses **(2).** Additionally, in both the United Kingdom and the United States it is the most common cause of acute liver failure as well in Egypt **(3).**

Although hepatotoxicity is more addressed than nephrotoxicity in paracetamol overdoses, paracetamol -induced renal damages, such as renal tubular damage and

acute renal failure are usually life-threatening and there is no specific treatment for them but there are protectants could prevent their happening **(4).**

The toxic dose of paracetamol is highly variable. The recommended maximum daily dose for healthy adults is 4 grams. Higher doses lead to increasing risk of toxicity. In adults, single doses above 10 grams or 200 mg/kg of body weight have a reasonable likelihood of causing toxicity **(5).** Toxicity can also occur when multiple smaller doses within 24 hours exceed these levels **(6).**

Toxicity of paracetamol is related to production of the reactive intermediate N-acetyl-p-benzoquinoneimine (NAPQI) by the hepatic cytochrome P450 system. When the production of NAPQI exceeds the capacity to detoxify it, as can occur in overdose, the excess NAPQI binds to cellular components and can cause death of hepatocytes **(7).**

Because APAP (acetyl-para-aminophenol) is a phenacetin metabolite, nephritic syndrome and renal papillary necrosis are possible (chronic analgesic nephropathy). In addition, patients at risk of increased NAPQI production as a result of CYP450 enzyme induction (from INH, rifampin, most anti-convulsants, ethanol) or reduced glutathione stores (alcoholism, HIV/AIDS, malnutrition, starvation) are at increased risk of hepatotoxicity from APAP **(8).**

MATERIALS AND METHODS

The study was performed according to The Institutional Review Board Zagazig University (ZU- IRB) instruction.

Experiments complied with the ARRIVE guidelines and was carried out in accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978).

The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University.

I-Chemicals used:

1- <u>Paracetamol</u>

Paracetamol ($C_8H_9NO_2$) (N-acetyl-p-aminophenol [APAP]), in the form of Cetal 500 mg tablets manufactured by EIPICO Company.

II- Experimental animals and dosing:

The present study was carried out on 14 adult healthy male albino rats with average age of 50-60 days, each weighing from 150 to 200 gm according to IRB instruction. They were obtained from the animal house unit in the Faculty of Medicine, Zagazig University. All animals were housed in environmentally controlled rooms, in wire mesh cages. They were kept under good hygienic conditions and fed on a balanced diet and tap water for two weeks before study. Temperature was maintained at 23±2°C. Later, these animals were equally divided into 2 groups (7 animals for each).

- **1st Group (control group)**: The rats received balanced diet and tap water.
- **2nd Group (paracetamol-treated group)**: The rats received a daily dose of paracetamol 2g/kg in 5 ml distilled water for 2 weeks. **(9)**

III- Experimental methods:

The body weight of rats in different groups was estimated initially at day 1 of the experiment before administration of food and drugs and daily till the end of the experiment using the same digital balance.

Venous blood samples were collected from animals by means of micro–capillary glass tubes from the retro–orbital plexus under thiopental anaesthesia as described by **Joslin (10)**.

The rats were sacrificed using cervical dislocation (breaking of the neck).

Kidneys were gently released from their fatty covering connective tissue and weighed by digital balance.

Each kidney was cut into two halves across the renal pelvis along its longitudinal axis to expose cortex, medulla and papilla. The specimens were immediately immersed in 10% formal saline for 48 hours to be processed and embedded in paraffin according to **Bancroft and Gamble (11).**

IV. <u>Morphometry:</u>

- Image analysis and morphometry was performed by ImageJ (FIJI) software. For the sections stained by Hematoxylin and eosin, Capillary tuft area (µm)2, Bowman space (µm)**,** proximal tubule diameter (µm) and distal tubule diameter (µm) were measured.
- The collected data were computerized and statistically analyzed using Graph Pad Prism 5.01. Quantitative data were expressed as mean ± SD (Standard deviation).
- Differences between mean values of experimental groups were tested with analysis of variance (ANOVA). Bonferroni's multiple comparison test was carried out as post hoc test of ANOVA.
- The results were considered statistically significant when the P value <0.05. Different stages of significance were considered. High significance (***) when P value < 0.001, Moderate significant (**) at 0.01 >P value >0.001 and low significance (*) when P value < 0.05. **(Table 4)**

V- Statistics:

- The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 18.0. Quantitative data were expressed as mean ± SD (Standard deviation).
- The results were considered statistically significant when the P value <0.05. Different stages of significance were considered. High significance (***) when P value < 0.001, Moderate significant (**) at 0.01 >P value >0.001 and low significance (*) when P value < 0.05.

RESULTS

I. Gross features:

- Final body weight showed highly statistical significant difference among different groups.
- Regarding kidney weight, there was statistical decrease in kidney weight in paracetamol treated group **(2nd group)** in comparison with control group.
- Concerning the comparison of final body weight of different groups, the 1st group, there was statistically significant difference with the 2nd group. As, body weights showed highly significant decrease in the paracetamol-treated group (2nd group). **(Table 1)**

II. Biochemical results

- concerning the kidney biochemical results, paracetamol-treated group showed highly significant increase.
- In current study, administration of paracetamol at dose 2g/kg in 5 ml distilled water orally **(2nd group)** significantly ($P \leq 0.05$) elevated serum Cr and BUN levels as compared to their respective levels in control group.
- There was statistically significant negative correlation between final body weight with serum creatinine and urea nitrogen level and statistically significant positive correlation with initial body weight and kidney weight **(Tables 2,3)**

III. Hematoxylin and eosin features

1st Group (control group):

Control group showed that the renal cortex was formed of renal corpuscles and tubules. Each renal corpuscle was consisted of a glomerulus containing tuft of capillaries. The renal corpuscle was surrounded by visceral and parietal layers of Bowman's capsule which were separated by Bowman's space. The outer parietal layer was formed of flat cells while the inner visceral layer was closely related to the glomerular capillaries. The cortical renal tubules were formed mainly of proximal and distal convoluted tubules **(Fig.1).**

The medulla of a rat kidney showed normal collecting tubules and loops of Henle with flat capillaries **(Fig.2).**

2nd Group (paracetamol-treated group):

There was congested renal blood vessel with markedly thick wall. Tubules showed necrotic epithelial lining cytoplasmic vacuolation. Disorganized tubules with desquamation in their epithelial lining were seen **(Fig.3)**. Remnant glomerulus and a shrunken degenerated glomerulus with dilated Bowman's space were noticed **(Fig.4).**

The medulla showed congested capillaries in the loops of Henle**,** vacuolated cells, some pyknotic nuclei in the tubules and dilated collecting ducts **(Fig.5).**

Table (1): Comparing final body weight between the 2 groups

Groups	Number of rats (14)	Final body weight mean ± SD (Range)	F-Test	p-value
1st group Control	7	227.1±15.7 (205-250)	19.6	**0.001****
2nd group Paracetamol	7	172.8±12.1 (159-191)		

* *Statistically highly significant difference (P ≤ 0.001)

Table (2): Comparing creatinine level between the 2 groups

Groups	Number of rats (14)	Serum creatinine mean ± SD (Range)	F-Test	p-value
1st group Control	7	0.27±0.08 (0.21-0.42)	5.9	**0.001****
2nd group Paracetamol	7	0.37±0.05 (0.3-0.44)		

* *Statistically highly significant difference (P ≤ 0.001)

Table (3): Comparing urea nitrogen level between the 2 groups

Groups	Number of rats (14)	Urea nitrogen level mean ± SD (Range)	F-Test	p-value
1st	7	11.8±0.47 (11.1-12.2)	16.9	**0.0001****
2nd	7	16.6±0.9 (15.1-17.8)		

* *Statistically highly significant difference (P ≤ 0.001)

Table (4): Morphometry table

Parameter Group	Capillary tuft area $(\mu m)^2$ Mean ± SD	Bowman space (µm) Mean ± SD	Prox. tubule diameter (µm) Mean ± SD	Dist. tubule diameter (µm) Mean ± SD
1st group Control	**1109.60±198.1**	**5.174±1.691**	**27.78±3.604**	**47.83±5.923**
2nd group Paracetamol	**641.3±102.1** **aa**	**9.785±2.265** **aaa**	**36.88±3.494** **aaa**	**67.32±7.703** **aaa**
F	**6.799**	**20.81**	**9.009**	**9.672**
P	**0.0001** ***	**< 0.0001** ***	**< 0.0001** ***	**< 0.0001** ***

(control group)

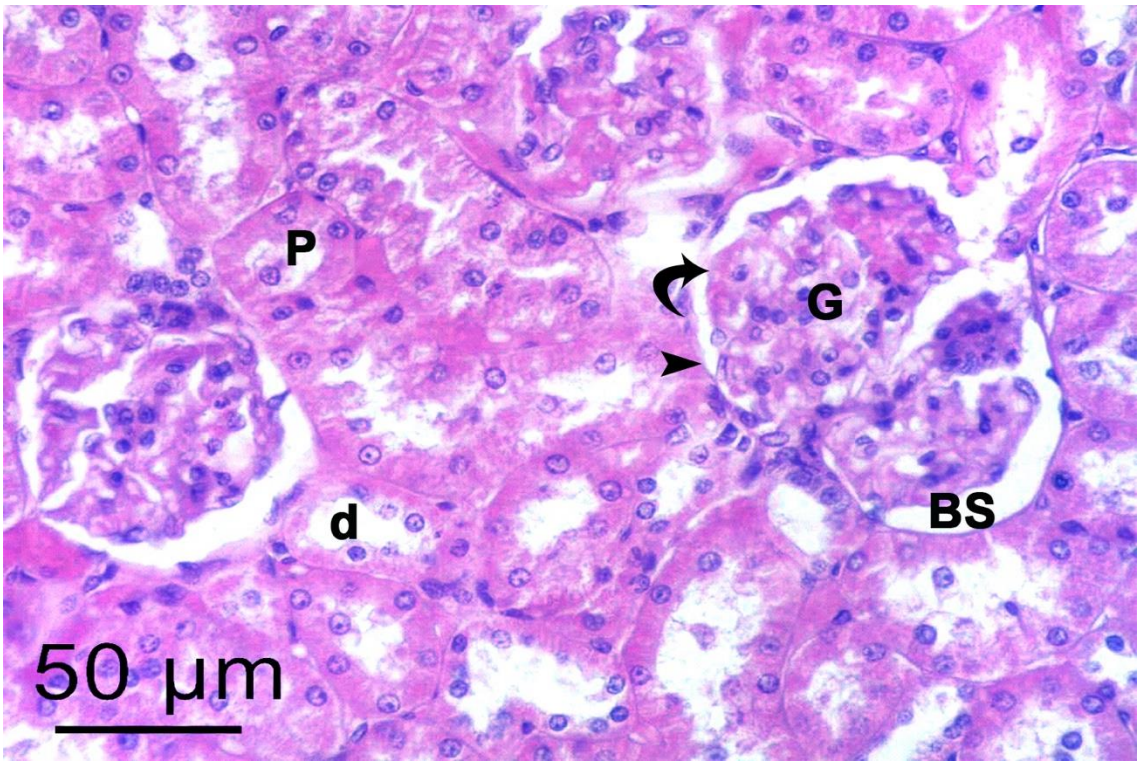

Fig. (1): A photomicrograph of a section of adult male albino rat kidney showing the glomeruli (G). The glomeruli are surrounded by visceral (curved arrow) and parietal (arrow head) layers of Bowman's capsule and separated by Bowman's space (BS). Proximal convoluted tubules with narrow lumen (p) and distal (d) convoluted tubules with wide lumen are also seen.

(H&E 400)

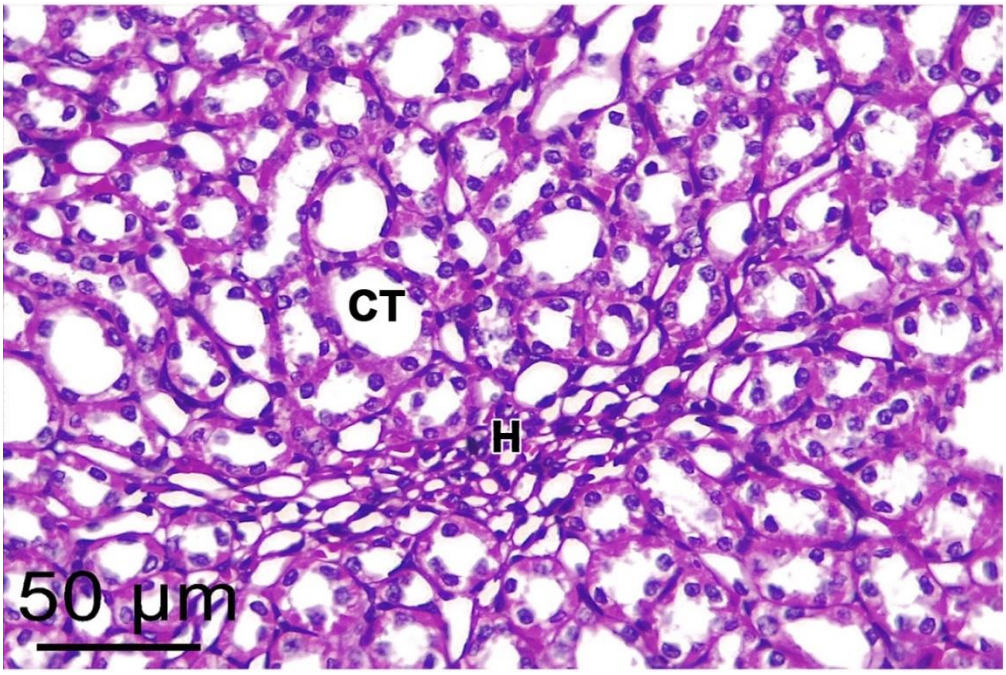

Fig. (2): A photomicrograph of a section in the medulla of a rat's kidney tissue showing normal collecting tubules (CT) and normal loop of Henle (H)with flat capillaries.

(H&E 400)

(paracetamol-treated group)

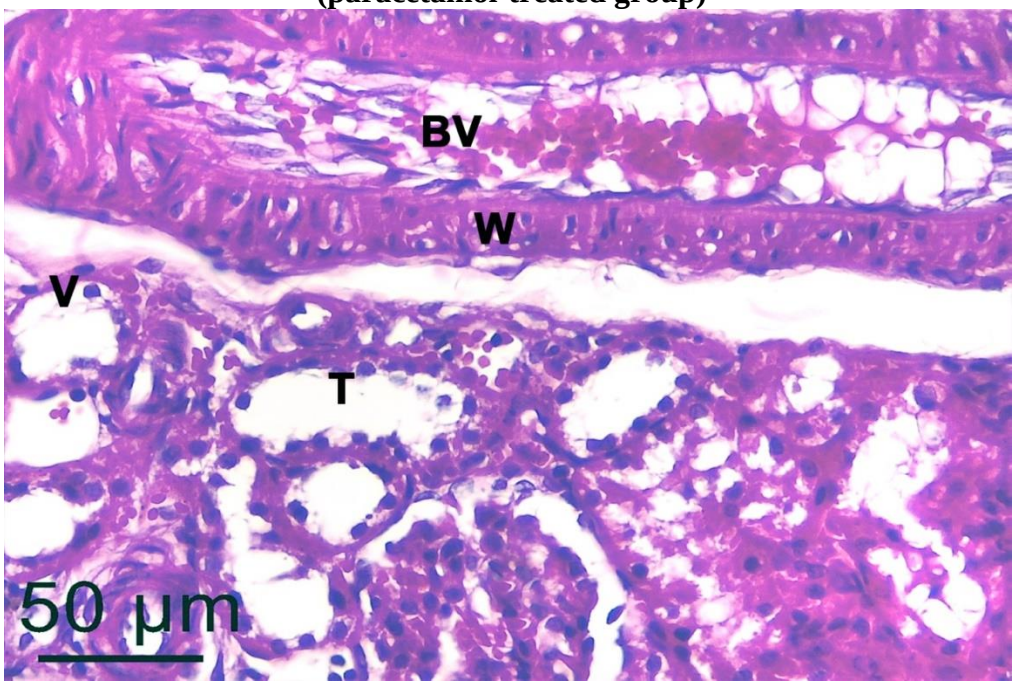

Fig. (3): A photomicrograph of a section of adult male albino rat kidney showing congested renal blood vessels (BV) with markedly thick wall (W). Tubules show dilatation (T) and cytoplasmic vacuolation (V).

(H&E 400)

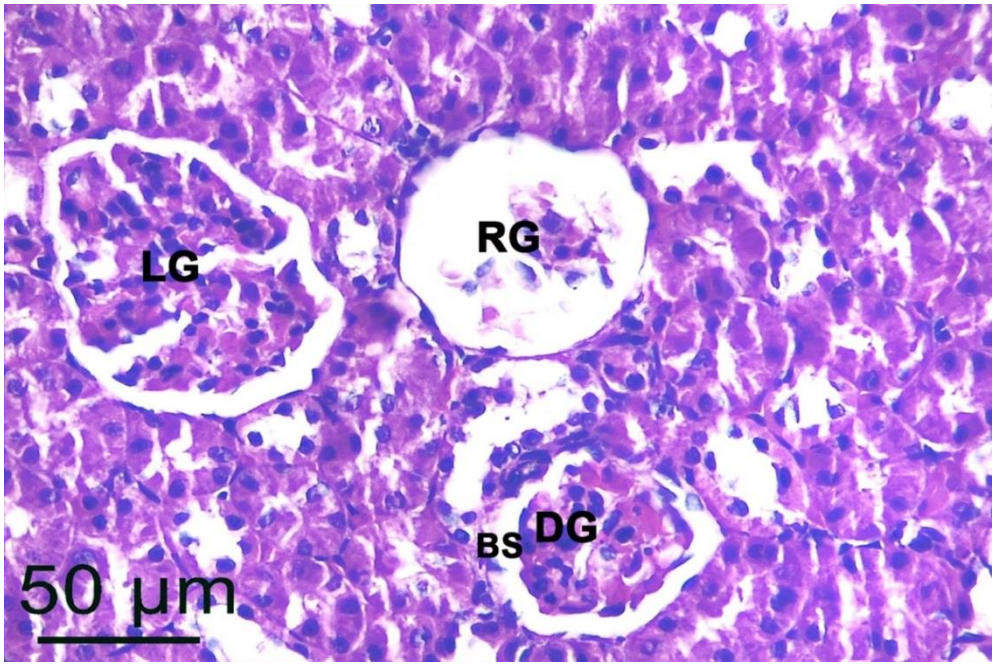

Fig. (4): A photomicrograph of a section of adult male albino rat kidney showing lobulated glomerulus (LG), remnant glomerulus (RG) can be noticed. A shrunken degenerated glomerulus (DG) with dilated Bowman's space (BS).

(H&E 400)

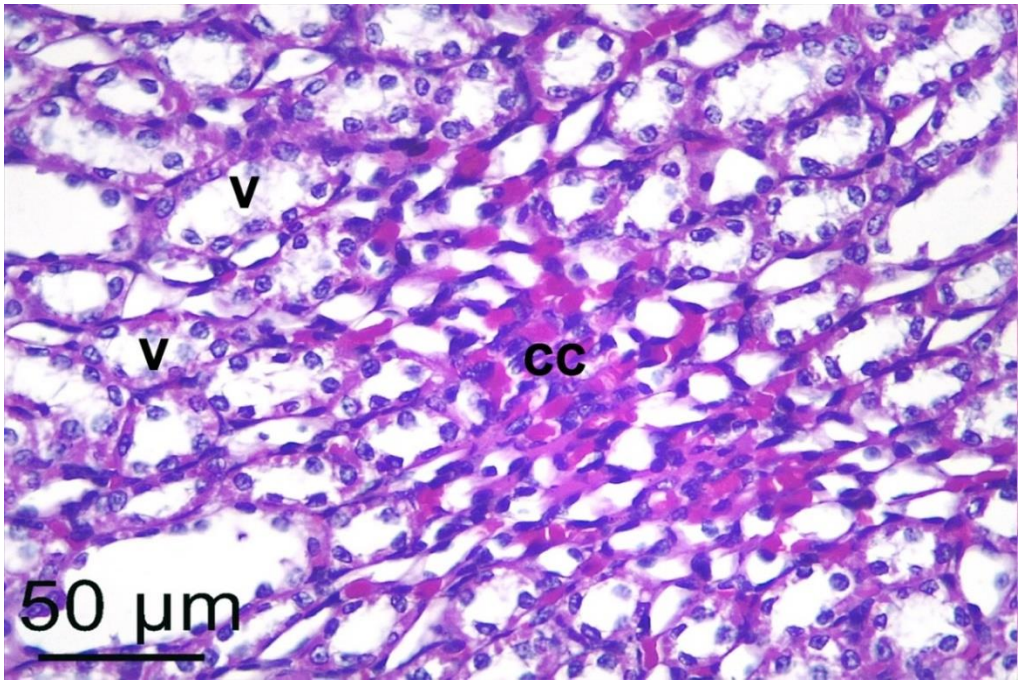

Fig. (5): A photomicrograph of a section in the medulla of a rat kidney showing congested capillaries (CC) and vacuolated cells (V).

(H&E 400)

DISCUSSION

In the current study, the paracetamol treated group showed a statistically significant decrease in the final body weight when compared with the control groups. This result was in accordance with **Patra et al (12)** who reported that in uremic control rats, the percentage of the increase in body growth was dramatically lesser than the other groups due to the toxicity of paracetamol, gastrointestinal toxicity, reduced feed and water intake. On the other hand, **Payasi et al (13),** who gave a very small dose of 66.6 mg/kg paracetamol infusion for 28 days, reported that there was no significant change in the mean body weight when compared with control group.

In the paracetamol treated group, the body weight gain of animals may be due to an increase in their appetite **(14,15).**

In current study, administration of paracetamol at dose 2g/kg in 5 ml distilled water orally significantly ($P \leq 0.05$) elevated serum Cr and BUN levels as compared to their respective levels in control group.

These results were in agreement with **Ijaz et al (16)** who reported that administration of paracetamol significantly ($P<0.05$) elevated serum Cr and BUN levels as compared to their respective levels in control group.

It was reported that paracetamol toxicity caused glutathione diminution and ultimately lipid peroxidation and starts its intracellular accumulation where its reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI), after making covalent bond with renal tissues, causes deterioration and death of cells which in turn is associated with electrolyte imbalance and creatinine and blood urea nitrogen instabilities. It has been documented that elevation in serum Cr and BUN were found to be more reliable and well reported parameters for scrutinizing the drug induced renal damage **(17,18).**

Even with a single oral dose of acetaminophen, BUN and serum creatinine significantly increased, as in **Das et al (19)** study on the male adult albino mice of Swiss strain and as with **Fouad et al (20)**.

The present study showed that paracetamol induced different histopathological changes in the renal cortex and medulla. Hypertrophy of renal glomeruli, hyper cellularity and congestion of glomerular capillaries observed in this study could be explained as mentioned by **Ahmed et al (21)** who stated that hypertrophy and severe congestion appeared in the glomerular tufts and the renal blood capillaries, with interstitial edema may be attributed to an increase in renal blood vessel permeability caused by a high dose of paracetamol. Also, **Aziz et al (22)** reported that the increased proliferation of mesangial cells leads to presence of hypercellular glomeruli in the renal cortex. On the other hand, some renal glomeruli in the present study showed glomerular atrophy. This may be attributed to a decrease in the glomerular filtration of the drug as a result of capillary constriction.

As regard to the renal tubules, there were tubular dilatation, tubular cell necrosis, sloughing of necrotic tubular epithelial cells into the lumens of tubules, marked cytoplasmic vacuolization and swelling of tubular cells and dark stained nuclei. These results were in accordance with **Kirbas et al (23)** who reported that an intensive deformation of epithelial cell structures of both proximal and distal tubules was observed. There were intensive degenerative structures related to the swelling of epithelial cells of the proximal tubules and there was cellular shedding of epithelium of the distal tubules due to the dilatations of the lumen and edematous fluid.

Morsy et al (24) reported the same results; they stated that exposure of epithelial cells to oxidant stress leads to an elevation in nitric oxide release and nitrite production and decrease in cell viability. Nitric oxide has a role in the acute renal failure because of its free radical nature; through its reaction with the superoxide radical, it probably generates the very cytotoxic peroxynitrite that could damage the tubular epithelium cells.

Also, this work demonstrated cytoplasmic vacuolization of tubular cells in the renal cortex of rats treated with paracetamol. These data could be explained by **Suriyakumari et al (25)** who demonstrated that cytoplasmic vacuolization occurs as one of primary responses to all forms of cell injury. They explained that increased permeability of cell membranes leads to an increase of intracellular water ending in cytoplasmic vacuolization.

In the present work, examination of kidney sections treated with paracetamol revealed also marked inflammatory cell infiltration. These results were in agreement with **Kumar et al (26). Pareta et al (27)** also stated that paracetamol treated group showed severe tubular necrosis, permeation of inflammatory cells, tubular deterioration, hemorrhage, distension of tubules and vacuolization.

Congested blood vessels with thickened wall observed in our study was in accordance with **Abd El-Twab et al (28**) who showed dilatation and congestion of renal blood vessels with leukocyte inflammatory cell infiltration.

In addition, **Kandemir et al (29)** added that kidney tissue showed increased pro-inflammatory cytokines such as renal tumor necrosis factor alpha (TNF-alpha), interleukin 1 beta (IL-1b) and interleukin 6 (IL-6) which could be another explanation of renal injury-induced by paracetamol.

On the contrary, Yousef et al (30) reported that paracetamol treatment at a dose of 650 mg/kg for 15days did not produce gross renal histological changes. Also, **Ahmed et al (31)** observed that the ingestion of paracetamol at a dose of 500 mg/kg /day for 30 days did not produce papillary necrosis or interstitial nephritis; however, it reduced the urinary concentrating ability of the animals.

In conclusion, it can be concluded that paracetamol administration produces marked degenerative changes in the histological structure of the kidney of adult male albino rats.

Conflict of Interest: NO
Financial Disclosures: NO

REFERENCES

1. **Bosch, M. E., Sanchez, A.J. R., Rojas, F. S. and Ojeda, C. B. (2006):** Determination of paracetamol: Historical evolution. Journal of Pharmaceutical and Biomedical Analysis; 42: pp. 291–321.
2. **Khashab, M., Tector, A.J. and Kwo, P.Y. (2007):** Epidemiology of acute liver failure. Current gastroenterology reports; 9 (1): pp. 66–73.
3. **Ryder, S.D. and Beckingham, I.J. (2001):** Other causes of parenchymal liver disease. BMJ (Clinical research ed.); 322 (7281): pp. 290–292.
4. **Peng H.C., Wang Y.H., Wen C.C., Wang W.H., Cheng C.C. and Chen Y.H. (2010):** Nephrotoxicity assessments of acetaminophen during zebrafish embryogenesis. Comparative Biochemistry and Physiology, Part C 151: pp. 480–486.
5. **Daly, F.F., Fountain, J.S., Murray, L., Graudins, A. and Buckley, N.A. (2008**): Guidelines for the management of paracetamol poisoning in Australia and New Zealand explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. The Medical journal of Australia; 188 (5): pp. 296–301.
6. **Watkins, P.B., Kaplowitz, N. and Slattery, J.T. (2006):** Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA: The Journal of the American Medical Association; 296 (1): pp. 87–93.
7. **Richard, C. D., Erdman, A. R., Olson, K. R., Christianson, G., Manoguerra, A. S., Chyka, P. A., Caravati, E. M., Wax, P.M., Keyes, D. C., Woolf, A. D., Scharman ,E. J., Booze, L. L. and Troutman, W. G. (2006):** Acetaminophen Poisoning: An Evidence-Based Consensus Guideline for Out-of-Hospital Management Clinical Toxicology. Taylor & Francis LLC; 44: pp.1–18.
8. **Diaz, J. (2006):** Acetaminophen (N-acetylpara-aminiphenol) (APAP) vs. Acetyl Salicyic Acid (ASA). In Color Atlas of Human Poisoning and Envenoming. By Diaz, J. (ed.), Taylor & Francis Group, New York; pp. 77-81.
9. **Canayakin, D., Bayir, Y., Kilic Baygutalp, N., Sezen Karaoglan, E., Atmaca, H. T., Kocak Ozgeris, F. B., Keles, M. S. and Halici, Z. (2016):** Paracetamol-induced nephrotoxicity and oxidative stress in rats: the protective role of Nigella sativa. Pharmaceutical biology, 54(10), 2082-2091.
10. **Joslin, J. O. (2009):** Blood collection techniques in exotic medicine. Journal of exotic Medicine, 18: 117-139.
11. **Bancroft, J. and Gamble, M. (2008):** Theory and Practice of Histological Techniques **6th edition.** Churchill Livingston.New York, Edinburgh, London. P:83-92.
12. Patra, A., Mandal, S., Samanta, A., Mondal, K. C., & Nandi, D. K. (2018). Therapeutic potential of probiotic Lactobacillus plantarum AD3 on acetaminophen induced uremia in experimental rats. Clinical Nutrition Experimental, 19, 12-22.
13. **Payasi, A., Chaudhary, M., Singh, B. M., Gupta, A. and Sehgal, R. (2010):** Sub-acute toxicity studies of paracetamol infusion in albino wistar rats. International Journal of Pharmaceutical Sciences and Drug Research, 2(2), 142-145.

14. **Mbikay, M. (2012):** Therapeutic potential of Moringa oleifera leaves in chronic hyperglycemia and dyslipidemia: a review. Front Pharmacol, 3: 24. doi:10.3389/fphar.
15. **Razis, A., Faizal, A., Ibrahim, M.D. and Kntayya, S.B. (2014):** Health benefits of Moringa oleifera. Asian Pac J Cancer Prev, 15: 8571-8576.
16. **Ijaz, A., Javed, I., Aslam, B., Khan, J. A., Khaliq, T., Khan, M. Z., Iqbal, Z., Naeem, M.A and Ashraf, M. M. (2016):** Nephroprotective and Antioxidant Effects of Moringa Oleifera (Sohanjna) in Paracetamol Induced Nephrotoxic Albino Rabbits. Pakistan Veterinary Journal, 36(3).
17. **Schnellman, R.G. (2001):** Toxic responses of the kidney. In: Casarett and Doull's Toxicology. The Basic Science of Poisons 6th.ed. By Klaassen, C. D. (ed.), McGraw-Hill Medical Publishing Division. New York, Chicago, San Francisco, Lisbon, London, Madrid, Mexico City, New Delhi, San Juan, Seoul, Singapore, Sydney, Toronto; pp. 491–514.
18. **Alderman, C. J., Shah, S., Foreman, J. C., Chain, B. M. and Katz, D. R. (2002):** The role of advanced oxidation protein products in regulation of dendritic cell function. Free Radical Biol Med, 32: 377-385.
19. **Das, J., Ghosh, J., Manna, P. and Sil, P. C. (2010):** Taurine protects acetaminophen-induced oxidative damage in mice kidney through APAP urinary excretion and CYP2E1 inactivation. Toxicology; 269: pp. 24–34.
20. **Fouad, A. A., Yacoubi, M. T. and El-Bidawy, M. H. (2009):** Therapeutic potential of hemin in acetaminophen nephrotoxicity in rats. Environmental Toxicology and Pharmacology; 27: pp. 277–282.
21. **Ahmed, W., Zaki, A. and Nabil, T. (2015):** Prevention of methotrexate-induced nephrotoxicity by concomitant administration of garlic aqueous extract in rat. Turkish journal of medical sciences, 45(3), 507-516.
22. **Aziz, H. O. A., Sarhan, N. I. and Abo-Elfadl, A. (2013):** Histological study of the protective role of curcumin versus ginger on renal corpuscles of carbon tetrachloride-treated mice. Egyptian Journal of Histology, 36(2), 336-345.
23. **Kirbas, A., Cure, M. C., Kalkan, Y., Cure, E., Tumkaya, L., Sahin, O. Z. and Pergel, A. (2015):** Effect of infliximab on renal injury due to methotrexate in rat. Iran J Kidney Dis, 9(3), 221-9.
24. **Morsy, M. A., Ibrahim, S. A., Amin, E. F., Kamel, M. Y., Rifaai, R. A. and Hassan, M. K. (2013):** Curcumin ameliorates methotrexate-induced nephrotoxicity in rats. Advances in pharmacological sciences**, 2013.**
25. **Suriyakumari, K. V. P., Udayakumar, R. and Ruba, T. (2016):** histological investigations on kidney of sildenafil citrate (edegra) treated albino mice. International Journal of Anatomy and Research, 4(1), 1977-80.
26. **Kumar, G., Hota, D., Saikia, U. N. and Pandhi, p. (2010):** Evaluation of analgesic efficacy, gastrotoxicity and nephrotoxicity of fixed-dose combinations of nonselective, preferential and selective cyclooxgenase inhibitors with paracetamol in rats. Experimental and Toxicologic Pathology, 62: pp.653-662.
27. **Pareta, S.K., Patra, K.C., Harwansh, R., Kumar, M. and Meena, K.P. (2011):** Protective effects of Boerhaaviadiffusa against acetaminophen induced nephrotoxicity in rats. Pharmacol Online, 2: 698-706.
28. **Abd El-Twab, S. M., Hozayen, W. G., Hussein, O. E. and Mahmoud, A. M. (2016):** 18 β-Glycyrrhetinic acid protects against methotrexate-induced kidney injury by up-regulating the Nrf2/ARE/HO-1 pathway and endogenous antioxidants. Renal Failure, 38(9), 1516-1527.
29. **Kandemir, F. M., Kucukler, S., Caglayan, C., Gur, C., Batil, A. A. and Gülçin, İ. (2017):** Therapeutic effects of silymarin and naringin on methotrexate-induced nephrotoxicity in rats: Biochemical evaluation of anti-inflammatory, antiapoptotic, and antiautophagic properties. Journal of food biochemistry, 41(5).
30. **Yousef, M. I., Omar, S. A. M.; El-Guendi, M. I. and Abdelmegid, L. A. (2010):** Potential protective effects of quercetin and curcumin on paracetamol-induced histological changes, oxidative stress, impaired liver and kidney functions and haematotoxicity in rat. Food and Chemical Toxicology; 48: pp. 3246–3261.
31. **Ahmed, M. H., Ashton, N. and Balment, R. J. (2003):** Renal function in a rate model of analgesic nephropathy: Effect of chloroquine. Journal of Pharmacology and Experimental Therapeutics.; 305: pp. 123–130.

How to Cite

Hegazy, A., Abd Al Hameed, E., El-Wafaey, D., Khorshed, O. Effect of Paracetamol administration on the Rat kidney structure: A Morphological Study. *Zagazig University Medical Journal*, 2021; (567-576): -. doi: 10.21608/zumj.2019.11494.1194