

The Structural and Functional Changes Induced By Lithium on The Renal Cortex of Growing Albino Rats: Ultrastructure and Laboratory Study

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ABSTRACT

Introduction: Lithium is a therapeutic agent currently used for the treatment of affective disorders controlling a variety of neurotic and psychosomatic manic depressions. The main objective of the present work was to demonstrate the histopathological effects of the therapeutic doses of Lithium on the renal tubules and glomeruli in growing albino rats. **Material and Methods:** Thirty growing male Sprague – Dawley albino rats were used in this study. The rats were divided into a control group formed of 6 rats and an experimental group formed of 24 rats which received a daily therapeutic dose of 20 mg Lithium/kg body weight by the same route for 7 weeks. The renal cortex in all animals is examined by light and electron microscopes. Blood was collected from the sacrificed animals for serum creatinine, urea, sodium and potassium to access the effect of lithium administration in a therapeutic dose on renal function. **Results:** The present work revealed that the therapeutic doses of Lithium induced nephrotoxicity in the form of degeneration and necrosis in the renal tubules and glomeruli. Alteration in the cellular fine structure and degenerated cytoplasm and cytoplasmic organelles were found revealing cellular degeneration and necrosis. Glomerulosclerosis and congestion were the predominant effect on the renal glomeruli. **Conclusion:** Histological and ultrastructural features of Lithium nephrotoxicity were detected in the current study with therapeutic doses of Lithium.

Keywords: Lithium, Renal cortex, Ultra-structure

INTRODUCTION

Lithium is a therapeutic agent currently used for the treatment of affective disorders controlling a variety of neurotic and psychosomatic manic depressions.¹ Extensive usage of Lithium and its compounds in pharmaceuticals, dehumidifying air conditioning units, ceramics, lubricants and many other chemical and biological laboratories brings this lightest alkali metal in close contact with man.² However, little work on its side effects, toxicity and carcinogenicity was published before the last decade.³ These authors found that Lithium salts caused ocular side effects, loss of body weight, cerebellar atrophy, respiratory problems, microcytic hypochromic anaemia and teratogenic effects as it could readily cross the placental barriers.

One of the frequent side effects of long term treatment with Lithium, even in therapeutic doses, was

nephrotoxicity.³⁻⁸ Moreover, the information available from the literature is controversial especially regarding the mechanism by which Lithium could produce its nephrotoxic effect. That a major biochemical action of Lithium in the kidney was competition with magnesium, thereby inhibiting magnesium dependent G proteins that activate vasopressin – sensitive adenylyl cyclase and increase intracellular cAMP level.⁹ The patients undergoing long term treatment with Lithium salts, developed nephrogenic diabetes insipidus, presented with polyuria and polydipsia due to a urinary concentrating defect that could lead to significant volume depletion.¹⁰⁻¹⁷ Moreover, the chronic Lithium treatment had been known to be associated with hyperchloremic metabolic acidosis.¹⁸ These authors demonstrated the underlying mechanisms for the impaired urinary acidification in the distal nephrons and collecting ducts. They detected that the expression of specific renal acid – base transporters was markedly altered in response to long – term Lithium treatment.

The long – term Lithium treated patients developed renal insufficiency exhibiting creeping creatinine phenomenon as their creatinine levels increased progressively.^{19,20} They found that Lithium affected the

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glomerular function reducing the glomerular filtration rate.

The effects of long term Lithium treatment in psychiatric patients, found that Lithium caused excess production of prostaglandins which decreased the ability of the kidney to reabsorb free water leading to nephrogenic diabetes insipidus.²¹

Recently, further investigations have been carried out on Lithium to evaluate its mechanism of nephrotoxicity. The Lithium could produce hyperparathyroidism and excess parathyroid hormone which could act as a partial agonist to arginine vasopressin and thereby inhibiting its hydro-osmotic action thus causing nephrogenic diabetes insipidus.²

The histopathological changes induced by Lithium toxicity in the renal tubules were studied by many researchers.^{23,24,15} Moreover, the predominant form of chronic renal disease associated with Lithium therapy was a chronic tubulointerstitial nephropathy including tubular atrophy and interstitial fibrosis, presented in the biopsies of renal tissues in long term Lithium treated patients.²³

The evaluated the appearance of Lithium nephropathy at magnetic resonance imaging showed that there were renal microcysts measuring from 1 to 2 mm diameter in both renal cortex and medulla in 16 patients with renal insufficiency.²⁴ The same authors, also found clinical and laboratory evidence of nephropathy secondary to long-term Lithium therapy.

Lithium was detected that it induced structural changes and affected the cell proliferation of renal tubules.¹⁵ These authors recorded that Lithium treatment dramatically reduced the fraction of principal cells of renal collecting ducts by quantitation of the cells in Wistar rats after four weeks of treatment with Lithium.

The long term effect Lithium treatment on the renal glomeruli in rat kidneys was studied by many authors.^{1,25,19} There was detectable hypertrophy of the renal glomeruli as a compensatory growth accomplished by an increase in the number of glomerular capillaries.¹ The net conclusion was that the Lithium caused marked decrease in the glomerular volume and shrinkage of the glomerular capillaries.²⁵ There was detectable mild degree of glomerulosclerosis in the renal glomeruli of the Lithium treated rats.¹⁹

There were deformative alterations in the renal tissues of rats after small therapeutic doses of Lithium treatment.²⁶ The authors found renal tubular necrosis and marked changes in the glomerular region represented by shrinkage in the glomerular capillary network.

Since there is only little information about the effects of Lithium on the structure and function of the kidney and its possible nephrotoxicity, therefore the aim of the current study is to elucidate the effects produced by Lithium in a therapeutic dose on the structure and function of the renal cortex of growing male albino rats in order to assess the safety of its administration.

MATERIALS AND METHODS

The current study was conducted on 30 adult male Sprague – Dawley albino rats weighing from 200 to 250 gm. All rats were kept in well-aerated metal cages under standard conditions. It was fed ad libitum and allowed free water supply. Lithium bicarbonate was dissolved in water to form Lithium chloride solution that was given orally to the experimental animals by gastric intubation. Each animal received a daily therapeutic dose of 20 mgm Lithium/kg body weight for 7 weeks.²⁷

The animals were divided into two groups as follows:

Group 1 (control group): formed of six rats which received no medication and lived in the same environment.

Group 2: formed of 24 rats which received an average of 2-2.5 ml of Lithium Chloride solution (20 mg of Lithium/kg body weight) for seven weeks.²⁷

Histological Study

At the end of the seventh week of the experiment, all the rats were sacrificed by cervical decapitation. The kidneys of the rats were dissected through a midline incision in their anterior abdominal walls. Each kidney was divided into two specimens for examination by light and electron microscope.

Preparation for examination by light microscope

Half of the kidney tissues were immediately fixed in 10% formal saline for 24 hours. The specimens were then thin trimmed, washed, dehydrated in ascending grades of alcohol, cleared in xylol and processed for paraffin sections of 6µm thickness. The obtained sections were stained with Hematoxylin and Eosin (Hx. and E.) for histological study.

Preparation for examination by electron microscope

The second half of the renal tissues were fixed in 3% glutaraldehyde with 0.1 phosphate buffer (at PH 7.2), for two hours at room temperature for electron microscope processing. Specimens are then post-fixed in 1% osmium tetra-oxide in phosphate buffer (at PH 7.2) for two hours for 4°C. Dehydration with ascending grades of ethanol then clearing using propylene oxide were performed before embedding the specimens in Epoxy resins.

Semi thin sections were cut at 1µm thickness by an ultra microtome then stained with toluidine blue. Ultrathin sections (50µm) were prepared and stained with uranyl acetate for 20 minutes and lead citrate for 10 minutes. These ultra thin sections were examined and photographed using transmission electron microscope (Zeiss, West Germany) in the histology department, faculty of medicine, Cairo university.

Laboratory Study

After scarification of the animals, blood was collected from their descending aorta. Serum was separated after centrifugation then transferred into clean plastic tubes and frozen at -20°C till the time of analysis. All samples were subjected to the following tests: serum creatinine and urea using (Dialab, Austria) semiautomated chemistry analyzer and serum sodium and potassium using (CIBA Corning) ion selective electrode analyzer. The data obtained were

subjected to statistical analysis using student's test. Values ≤ 0.05 were regarded as significant.

RESULTS

The results of the current study showed the histological ultrastructural and biochemical changes in the kidney of the male growing albino rats under the effect of oral administration of Lithium for 7 weeks.

HISTOLOGICAL RESULTS

Light microscopic examination:

Control group

The renal tissue of the control rats was noticed to be composed of proximal convoluted tubules lined with a single layer of columnar epithelial cells, resting on a basement

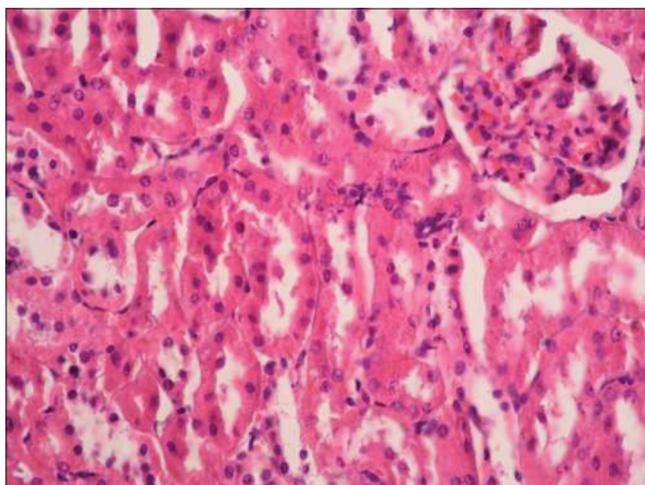


Figure 1: A photomicrograph of a section of a renal cortex of a control male albino rat, showing normal structure of the glomerulus, proximal and distal convoluted tubules and Bowman's space. (Hx. & E.; x 400)

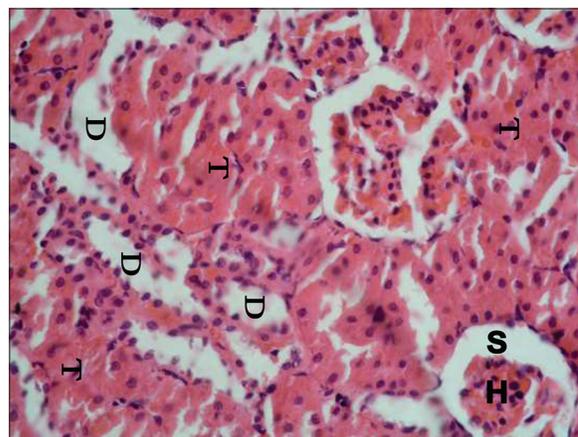


Figure 3: A photomicrograph of a section in the renal cortex of a rat after 7 weeks of oral intake of Lithium, showing atrophic tubules (T) and dilated tubules (D) with degeneration of the tubular epithelium. Focal glomerulosclerosis characterized by homogenous eosinophilic areas (H) and shrinkage of the capillary network resulting in widening the space (S) seen in part of the section (Hx. & E.; x 400)

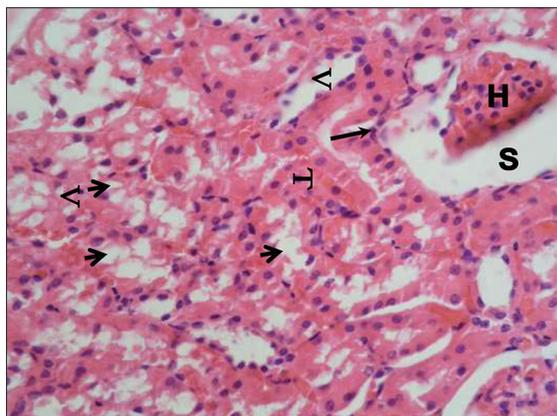


Figure 2: A photomicrograph of a section of a renal cortex of a rat after 7 weeks of oral intake of Lithium, showing atrophic tubules (T) in the form of necrosis of the epithelial cells (arrow), collapse of the lumen and cytoplasmic degeneration as shown by its vacuolization (V) and (arrows heads). The glomerulus shows glomerulosclerosis characterized by homogenous eosinophilic areas (H) and shrinkage of the capillary network resulting in widening the space (S). (Hx. & E.; x 400)

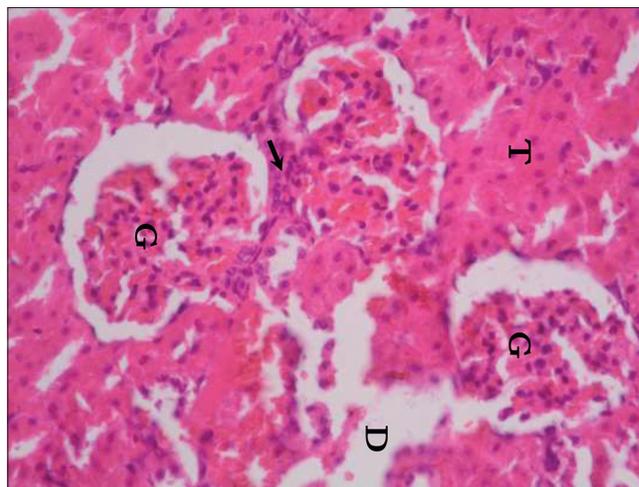


Figure 4: A photomicrograph of a section in a renal cortex of a rat after 7 weeks of oral intake of Lithium, showing atrophic tubules (T), dilated tubules (D) and degenerated glomeruli (G). Note the excess interstitial cellular infiltration (arrow) (Hx. & E.; x 400).

membrane. Each columnar cell contained a single basal spherical nucleus with bright pink cytoplasm deeply stained with eosin stain. The distal convoluted tubules were lined with cuboidal cells. Their nuclei were smaller and central and the cytoplasm was lightly stained. The glomeruli appeared in the cortex, made up of capillaries which were lined with endothelial cells. The tuft of glomerular capillaries was enveloped with Bowman's capsule, which was a double layered cup lined with squamous epithelium (Fig.1).

Experimental group

Examination of the renal tissue of the rats after 7 weeks oral Lithium administration of its therapeutic dose revealed degeneration and necrosis of the tubules and glomeruli.

The predominant histopathological findings observed in the present study were features of tubular necrosis.

Atrophic tubules (Figs. 2,4,5,6, 7) appeared with exfoliation of the lining epithelial cells and cytoplasmic degeneration (Figs. 2,6,7). Dilated tubules were detected also lined with exfoliated tubular epithelial cells (Figs. 3,5,7).

Separation of the tubular epithelial cells from the basement membrane was noticed in the tubules and vacuolization of the cellular cytoplasm also appeared in the epithelial cells (Figs. 2,6,7).

The glomeruli showed focal areas of glomerulosclerosis, characterized by glomerular shrinkage (Figs. 2,5,7). Shrinkage of the capillary network resulted in widening of the glomerular space between the wall and the network (Figs. 2,5,7). Peritubular congestion (Fig. 7) was also seen by light microscopic examination.

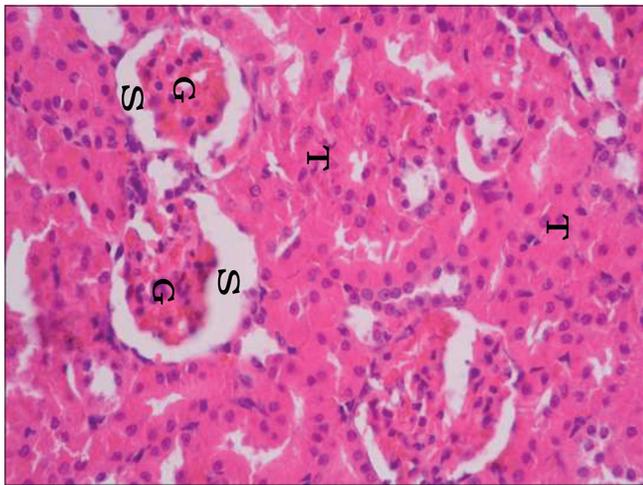


Figure 5: A photomicrograph of a section in the renal cortex of a rat after 7 weeks of oral intake of Lithium, showing marked shrinkage of the glomeruli (G) leading to widening of Bowman's space (S) distortion and atrophic tubules (T) (Hx. & E.; x 400)

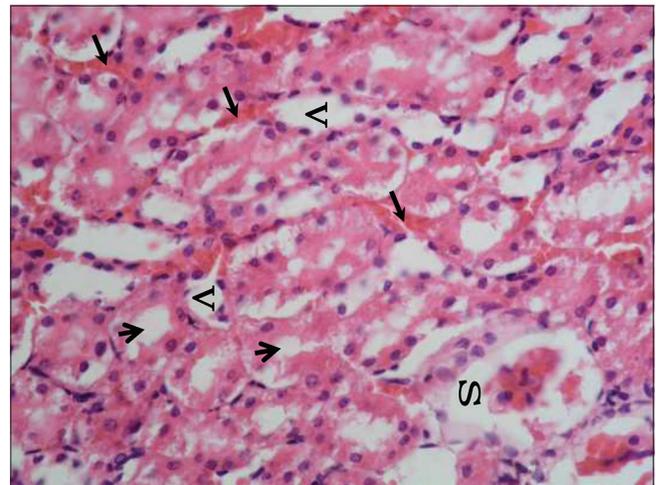


Figure 7: A photomicrograph of a section in the renal cortex of a rat after 7 weeks of oral intake of Lithium, showing interstitial congestion (arrows) cytoplasmic vacuolization (V) and (arrow heads) with widening of the Bowman's space (S) (Hx. & E.; x 400) .

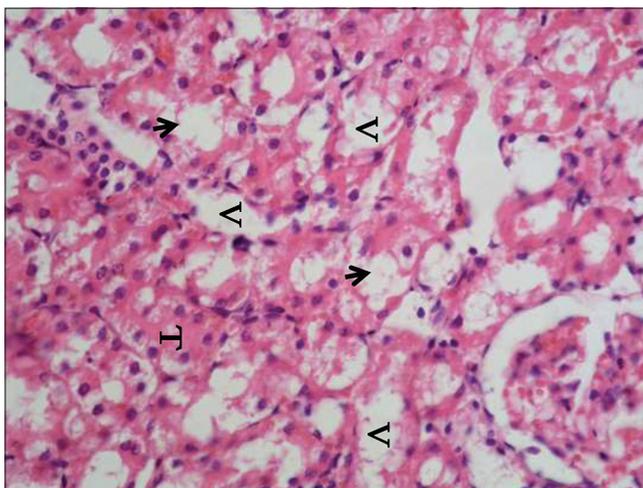


Figure 6: A photomicrograph of a section in the renal cortex of a rat kidney after 7 weeks of oral intake of Lithium, showing atrophic tubules (T) with vacuolization of the cytoplasm of the tubular epithelium (V) and (arrow heads) (Hx. & E.; x 400)

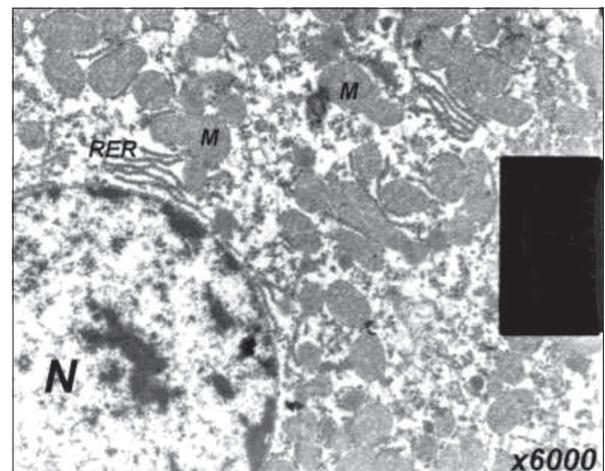


Figure 8: TEM of the renal cortex of a control rat, showing columnar epithelial cells of a proximal convoluted tubule. Their nuclei (N) are large, basal and spherical with peripheral chromatin condensations. The cytoplasm contained mitochondria (M). Note the clear rough endoplasmic reticulum (RER) (Hx. & E.; x 4000).

Electron microscopic examination

Control group

Electron microscopic examination of the renal sections of the control rats revealed the normal ultrastructural features of the tubular epithelial cells and glomeruli. The columnar epithelial cells of the proximal convoluted tubules showed rounded nucleus, abundant mitochondria scattered in the cytoplasm, thin regular basement membrane and intact apical microvilli. (Figs. 8,11,12).

Experimental group

Electron microscopic examination of the renal tissues revealed alteration in the tubular epithelial fine structure.

Excess dense lysosomal bodies were detected in the cytoplasm of the renal tubules (Figs. 13, 15, 17). The cytoplasm of the tubules showed different density and vacuolization (Figs. 13, 14,15,16,17).

Excess dense, swollen sometimes vacuolated and elongated mitochondria were found in the cytoplasm (Fig. 14, 15).

The cisternae of the rough endoplasmic reticulum showed obvious fragmentation with partial loss of their ribosomes (Fig. 9).

Glomerulosclerosis was detected in the renal tissues with thickened basal lamina of the glomeruli (Fig.14, 15). Fusion of the foot processes of the podocytes was noticed (Fig. 16).

Laboratory Results

There were insignificant differences for all the investigated parameters for the control group1 (Table 1,2).

In the experimental Group2 there was a significant increase in the serum levels of creatinine, urea, sodium

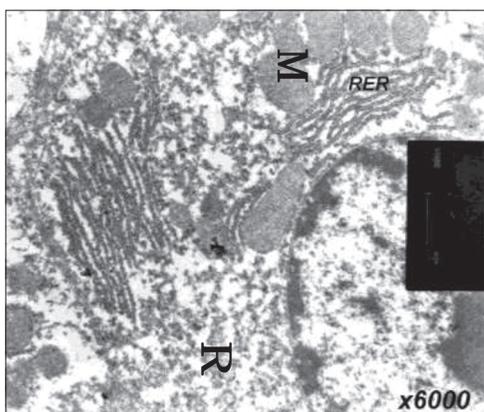


Figure 9: TEM of the renal cortex of a rat after 7 weeks of oral intake of Lithium, showing a proximal convoluted tubule. The cytoplasm contains numerous electron dense mitochondria (M) some of which are in their dividing stage. Fragmented cisternae of rough endoplasmic reticulum (RER), with scattered ribosomes (R) (EM x 6000)

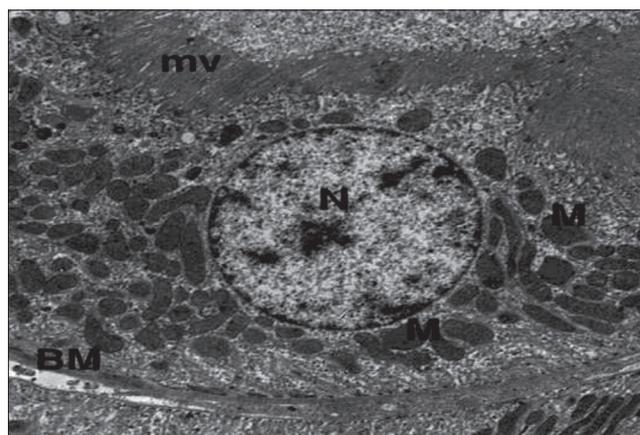


Figure 11: TEM of the renal cortex of a part of a proximal convoluted tubule of a rat kidney of the control group showing the epithelial lining cell with rounded nucleus (N). There are abundant mitochondria (M). Thin regular basement membrane (BM) and intact apical microvilli (mv) (E.M. ; X 5000)

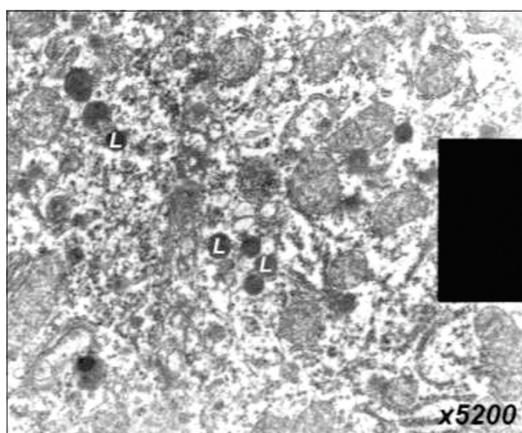


Figure 10: TEM of the renal cortex of a control rat after 7 weeks of oral intake of Lithium showing part of a proximal convoluted tubule with dense heterogenous bodies mostly lysosomes (L) (X 5200)

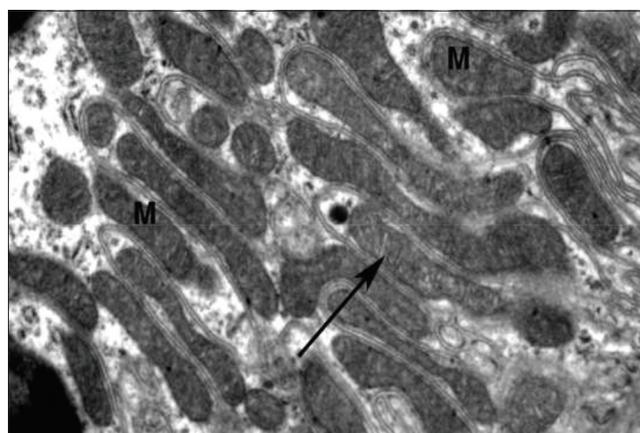


Figure 12: TEM of the renal cortex of a part of a proximal convoluted tubule of a rat kidney of the control group showing abundant mitochondria (M) with intact cristae (arrow) of one of the epithelial lining cells (E.M. ; X 8000).

and potassium as compared to the control Group1 (Figs.18, 19, 20, 21).

DISCUSSION

The toxic effects on the tubular epithelial cells found in the current study were presented by tubular atrophy, dilated tubules, exfoliation and separation of their lining epithelial cells from the basement membrane. Vacuolization and degeneration of the cytoplasm were detected in the present study. Peritubular infiltration with lymphocytes and mononuclear cells were also noticed.

In the current study, it was detected that nephrotoxicity, induced by Lithium therapy, could be caused by the therapeutic dose of Lithium salts. Our study was in good agreement with²³ and were also supported by the findings

of²⁶ as they detected chronic tubulo-interstitial nephropathy after long term Lithium treatment in human and rats respectively.

The ultrastructural changes affecting the proliferation of the renal tubular cells detected by¹⁵ were parallel to the findings of the current study. The observations of the present study concerning the changes in the tubular epithelial cells were presented by alteration in the cellular fine structure with complete loss of the apical brush border due to loss of the apical microvilli. The cytoplasm appeared with different density and contained excess dense lysosomal bodies and vacuoles. Degenerated cytoplasm was found revealing cellular degeneration and necrosis. Degenerated cytoplasmic micro-organelles were detected in the current study such as fragmented cistern of rough endoplasmic reticulum and excess dense, swollen and

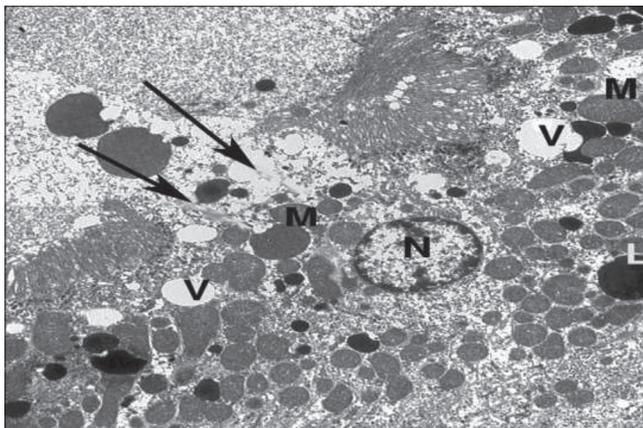


Figure 13: TEM of the renal cortex of a part of a proximal convoluted tubule of a rat kidney specimen after 7 weeks of oral intake of Lithium showing partial loss of the apical microvilli (arrows), large lysosomes (L) and cytoplasmic vacuoles (V). Variable sizes mitochondria (M) and small size nucleus (N) can be seen (E.M ; X 5000)

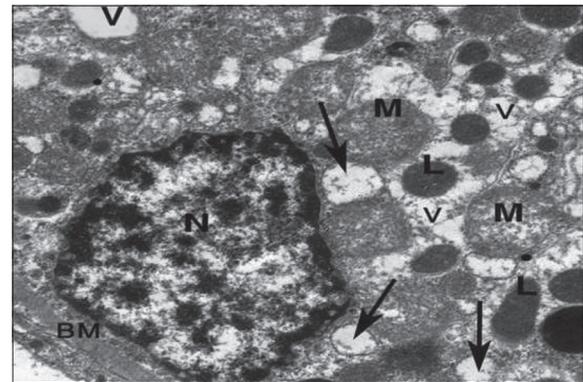


Figure 15: TEM of the renal cortex of a part of lining epithelium of a proximal convoluted tubule of a rat kidney after 7 weeks of oral intake of Lithium showing distorted nucleus (N) with clumped chromatin material. Vacuolization of the cytoplasm (V) and many large lysosomes (L) can be observed. Mitochondria (M) are vacuolated, with loss of their cristae (arrows). Thickening of the tubular basement membrane (BM) can be noticed (E.M ; X 8000)

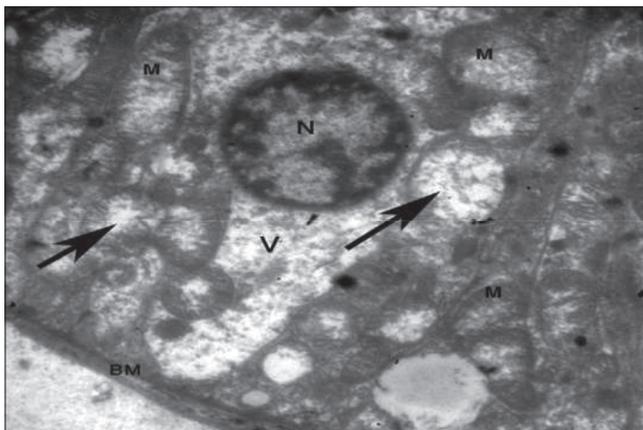


Figure 14: TEM of the renal cortex of the renal cortex of a rat after 7 weeks of oral intake of Lithium, showing one tubular epithelial cell of a proximal convoluted tubule showing dark nucleus (N) with condensed chromatin. The cytoplasm marked with number of heterogenous irregular multiple cytoplasmic vacuoles (V) and numerous swallowed of the mitochondria (M) with loss of their cristae (arrows). Thickening of the tubular basement membranes (BM) is also seen (E.M ; X 8000)

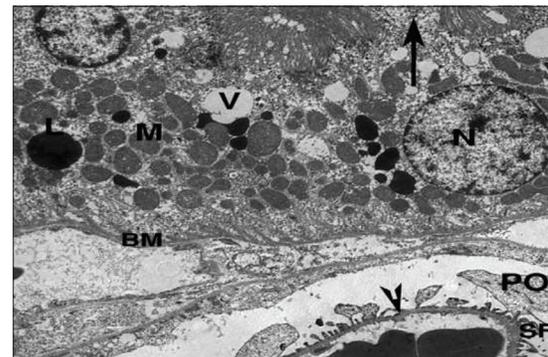


Figure 16: TEM of the renal cortex of a part of lining epithelium of a proximal convoluted tubule of a rat kidney after 7 weeks of oral intake of Lithium showing a part of a glomerulus and part of proximal convoluted tubule. The glomerulus shows a podocyte (PO) with secondary foot processes (SF). Area of the secondary foot processes (arrowhead) can be noticed. The lining epithelium of the proximal convoluted tubule shows normal nucleus (N) and mitochondria (M) and thin basement membrane (BM). Area of lost apical microvilli (arrow), number of heterogenous irregular bodies dense bodies mostly lysosomes (L) in the cytoplasm and some vacuoles (V) (E.M.; X 5000)

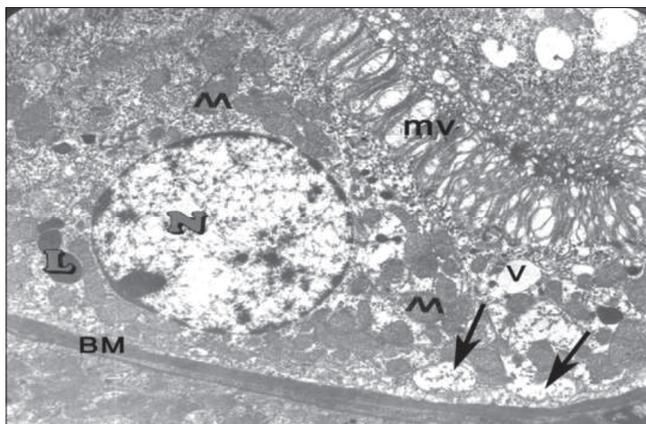


Figure 17: TEM of the renal cortex of a rat after 7 weeks of oral intake of Lithium, showing part of the epithelial cells of a proximal convoluted tubule. Evidence of cytoplasmic degeneration was seen in the form of pleomorphic vacuoles (V) and heterogenous irregular dense bodies mostly lysosomes (L) normal nucleus (N) and intact apical microvilli (mv) as well as uniformly thin basement membrane (BM) can be seen. Few mitochondria (M) showed loss of their cristae (arrows), (E.M ; X 5000)

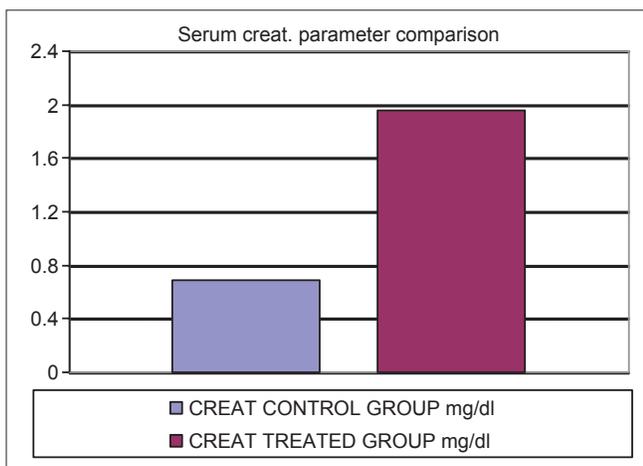


Figure 18: The serum creatinine level before and after the treatments

Table 1: The summary of data for all groups control and treated for the parameters measured
By applying independent sample t-test (which permits to use different sample size for comparison)

	N	Mean	SD	SEM
Creat control group	6	0.690	0.0400	0.0163
K control group	6	4.033	0.1033	0.0422
Na control group	6	140.0	0.6325	0.2582
Urea control group	6	33.50	1.9748	0.8062
Creat treated group	24	1.958	0.1932	0.0394
K treated group	24	8.908	0.2083	0.0425
Na treated group	24	170.083	1.8396	0.3755
Urea treated group	24	72.625	3.3338	0.6805

elongated mitochondria. Thickened basal lamina of the tubular epithelial cells was also found.

There was no interstitial fibrosis found in the present study as detected by²³, may be because we performed our

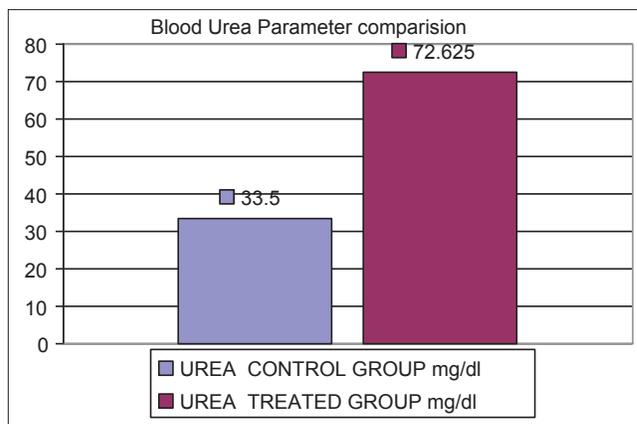


Figure 19: Blood Urea level measured after and before the treatment

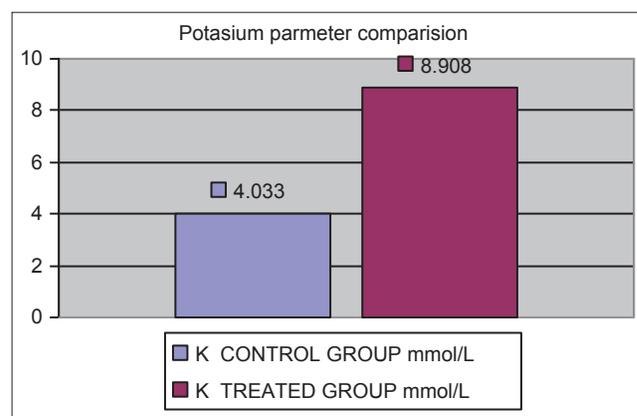


Figure 20: Serum Potassium level measured after and before the treatment

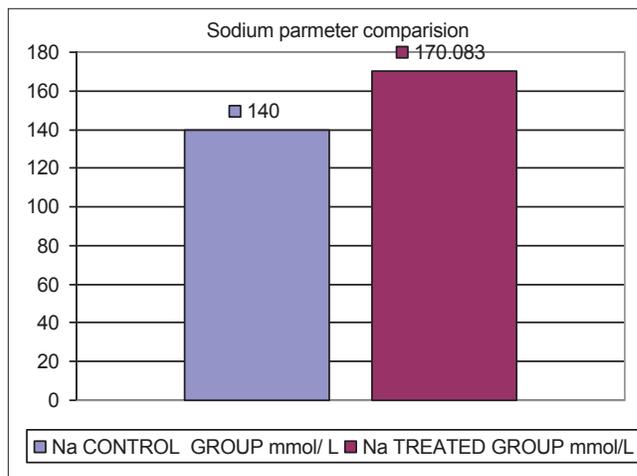


Figure 21: Serum Sodium level measured after and before the treatment

experiment in seven weeks while they did it in six months. Also no renal microcysts were noticed in the cortex nor the medulla as found by.²⁴

The glomerular changes developed in the experimental rats of the current study were characterized by glomerulosclerosis. Hyaline insudation, thickening in the basal lamina of the

Table 2: The P values for the comparison of the data measure after and before treatment

	Creatinine control group	K control group	Na control group	Urea control group
Creatinine. treated group	P<0.0001			
K treated group		P<0.0001		
Na treated group			P<0.0001	
Urea treated group				P<0.0001

glomeruli and fusion of the foot processes of the podocytes were detected by the electron microscope in the present study. These findings were parallel to those found by.¹⁹

Shrinkage of the glomeruli and shrinkage of the capillary network resulting in widening the space between the wall and the network were found in the current study as proved by.^{25,26} Nevertheless, hypertrophy of the renal glomeruli as a compensatory growth in some of them with an increase in the number of glomerular capillaries was detected¹.

Moreover, peritubular congestion and congested glomeruli were found in the present study.

In conclusion, Histological and ultrastructural features of Lithium nephrotoxicity were detected in the current study with therapeutic doses of Lithium. This nephrotoxicity was presented by tubular epithelial necrosis, glomerular and vascular diseases.

As physicians frequently keep their patients on long term Lithium therapy, they should be aware of the numerous side effects and pathogenesis of this drug. Strategy for detection of these side effects by regular investigations and managements are needed in Lithium therapy.

CONCLUSION

In conclusion, Histological and ultrastructural features of Lithium nephrotoxicity were detected in the current study with therapeutic doses of Lithium. This nephrotoxicity was presented by tubular epithelial necrosis, glomerular and vascular diseases.

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REFERENCES

- Marcussen N, Nyengaard, JR. and Christensen S. Compensatory growth of glomeruli is accomplished by an increased number of

- glomerular capillaries. Lab. Invest. 1994; 70(6): 868 – 74.
- Shirley DG, Walter S J, Skinner J. and Noormohamed, F. H. The natriuretic effect of lithium in man: is the proximal tubule involved? Scand. J. Clin. Lab. Invest. 1995; 55(7): 635 – 42.
- Carney S. and Jackson, P. Acute lithium administration impairs the action of parathyroid hormone on rat renal calcium, magnesium and phosphate transport. Clin. Exp. Pharmacol. Physiol. 1998; 25(10): 795 – 9.
- Coskunol H, Vahip S, Mees E D. Basci, A, Bayindir, O. and Tuglular, I. Renal side effects of long term lithium treatment. J. Affect Disord. 1997; 43(1): 5 – 10.
- Thompson CJ, France AJ. and Baylis PH. Persistent nephrogenic diabetes insipidus following lithium therapy. Scott. Med. J. 1997; 42(1): 16 – 7.
- Wolf ME, Moffat M, Mosnaim J. and Dempsey S. Lithium therapy, hypercalcemia, and hyperparathyroidism. Am. J. Ther., 1997; 4(9); 323 – 5.
- Gitlin M. Lithium and the kidney: an updated review. Drug Saf. 1999; 20(3): 231 – 43.
- Stone K A. Lithium – induced nephrogenic diabetes insipidus. J. Am. Board Fam. Pract. 1999; 12(1): 43 – 7.
- Oakly P W, Dawson AH. and Whyte IM. Lithium: Thyroid effects and altered renal handling. J. Toxicol. Clin. Toxicol. 2000; 38(3): 333 – 7.
- Bendz H, Aurell M. and Lanke J. A historical cohort study of kidney damage in long term lithium patients: Continued surveillance needed. European Psychiatry. 2001; 16(4): 199 – 206.
- Stoll P M, Stokes P E. and Okamoto M. Lithium isotopes: differential effects on renal function and histology. Bipolar. Disord. 2001; 3(4): 174 – 80.
- Llagan, MC, Carlson D. and Madden JF. Lithium toxicity: two case reports. Del. Med. J. 2002; 74(6): 263 – 70.
- Yuan S. Vaughan M. and Agoff, SN. Left – sided splenorenal fusion with marked extramedullary hematopoiesis and concurrent lithium toxicity. Archives of Pathology and Laboratory Medicine. 2002; 127(1): 1 – 3.
- Chmielnicka J. and Nasiadek M. The trace elements in response to lithium intoxication in renal failure. Ecotoxicol. Environ. Saf. 2003; 55(2): 178 – 83.
- Christensen BM, Marples D, Kim Y, Wang W, Frokiaer J. and Nielsen S. Changes in cellular composition of kidney collecting duct cells in the rats with lithium induced nephrogenic diabetes insipidus. Am. J. Physiol. Cell Physiol. 2004; 286: C952 – C964.
- Christensen BM, Kim Y H, Kwon TH. and Nielsen S. Lithium treatment induces a marked proliferation of primarily principal cells in rat kidney inner medullary collecting duct. Am. J. Physiol. Renal Physiol. 2006; 24: 1 – 9.
- Nielsen J, Kwon T.H, Frokiaer J, Knepper MA. and Nielsen S. Lithium – induced nephrogenic diabetes insipidus in rats is associated with loss of alpha – ENaC regulation by aldosterone in NaCl cotransporter. Am. J. Physiol. Renal Physiol. 2006; 290(5): F1222 – 33.
- Kim Y, Kwon T, Christensen BM, Nielsen J, Wall SM, Madsen K M, Frokiaer J. and Nielsen S. Altered expression of renal acid – base transporters in rats with Lithium induced nephrogenic diabetes insipidus. Am. J. Physiol. Renal Physiol. 2003; 285: F1244 – 57.
- Skyum H, Marcussen N, Nielsen SH. and Christensen S. Interstitial capillary changes in lithium nephropathy: effects of antihypertensive treatment. APMIS. 2004; 112(10): 686 – 97.
- Lepkifker E, Sverdlik A, Lancu I, Ziv R, Segev S. and Kotler M. Renal insufficiency in long term lithium treatment. J. Clin. Psychiatry. 2005; 66(3): 398 – 9.
- Tran – Van D, Avargues P, Labadie P, Herve Y, Dardare, E. and Fontaine B. Intravenous ketoprofen for severe lithium induced

- polyuria. *Presse Med.* 2005; 34(16): 1137 – 40.
22. Livingstone C. and Rampes H. Lithium: A review of its metabolic adverse effects. *J. Psycho pharmacol.* 2006; 20(3): 347 – 55.
23. Kanfer A, and Blondiaux I. Renal and metabolic complications of lithium. *Nephrologie.* 2000; 21(2): 65 – 70.
24. Farres MT, Ronco P, Saadoun, D, Remy P, Vincent F Khalil A. and Le blanche A F. Chronic lithium nephropathy. MR Imaging for diagnosis. *Radiology.* 2003; 229: 570 – 4.
25. Min G, Christensen S, Marcussen N. and Osterby R. (2000); Glomerular structure in lithium – induced chronic renal failure in rats. *APMIS.* 2003; 108(10): 652 – 62.
26. Sharma SD. and Iqbal M. Lithium - induced toxicity in rats: A hematological, biochemical and histopathological study. *Biol. Pharm. Bull.* 2005; 28(5): 834 – 7.
27. Marples D, Christensen S, Christensen E. I, Ottosen PD. and Nielsen S. Lithium induced down regulation of aquaporin 2 water channel expression in rat kidney medulla. *J. Clin. Invest.* 1995; 95: 1838 – 1845.

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