



Research Article

Histological Study On Kidney Affected By Carbamazepine Drug In Postnatal Rat

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ABSTRACT

Background: The use of antiepileptic drugs (AEDs) during pregnancy warrants several side effects and also deleterious effects on fetal development, the antiepileptic drugs have potential to affect the fetal development throughout the pregnancy although, the majority of infants born to epileptic pregnant women are normal but more expose to the malformations. **Aim:** The present study aimed to investigate the effect of carbamazepine drug on the kidney development at day 7 postnatally in the Albino Rat (*Rattus rattus*) as a mammalian model. **Material & Methods:** 20 healthy pregnant female rats were divided into two groups, 10 pregnant rats in each group; group one served as control group administrated distal water while group two used as experimental group which administrated carbamazepine drug at dose 20mg/kg/rat daily from first day of pregnancy till 7th day after birth in both groups. On 7th day after birth, the newborns and kidneys were

removed; the weight is measured and then fixed, dehydrated in ascending grades of alcohol, cleared in xylene and infiltrated with filtered paraffin. The paraffin blocks were made and 5µm thin sections were obtained using a rotary microtome. The sections were stained with H&E stain, PAS examined under light microscope and scanning electron microscope (SEM). **Results:** Under the light microscope, the kidney in Group II show the glomerular atrophy with enlargement of Bowman's space, hemorrhage, congestion, degeneration and hypertrophy of simple squamous epithelial lining cells of partial layer of Bowman's capsule, glomerular cells accumulation, detachment of tubular epithelial lining cells from basement membrane and tubular degeneration represented by (cell swelling, loss nucleus and cell death); a statistically significant differences have been shown in the diameter of renal corpuscle, glomerular tuft and Bowman's space, and also in the renal tubules proximal and distal convoluted tubules ($p < 0.001$). The results of scanning electron microscope found that the visceral layer of renal corpuscle contain specialized cells called podocyte cells and the diameter of these cells is statistically significant in treated group in comparison to control group ($p < 0.001$), while There is no significant differences found in the weight of kidneys and newborns. **Conclusion:** The results of the present study indicated that carbamazepine drug administration to the dams produced teratogenic effects on the developing of kidney in rat.

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INTRODUCTION

During pregnancy, the proper use of medications is an essential part of prenatal care, while these medications can effect on the health of the pregnant women and developing fetus which is exposed to a variety range of adverse effects.[1,2] About 8% of pregnant women need permanent drug treatment due to the chronic diseases and pregnancy related complications.[3] Epilepsy is a common serious medical neurological condition characterized by spontaneous tendency for recurrent seizures, an epileptic seizure is a single event that occurs when a strong surge of electrical activity causes the abnormal and excessive discharge of set of neurons in the brain resulting to variety of clinical sings.[4] Anticonvulsants are known as teratogens such as Carbamazepine (CBZ) is most widely used as antiepileptic drug in the clinic since 1965.[5] It is highly effective for the treatment of partial seizures and generalized tonic- clonic seizures, trigeminal neuralgia and mood disorders. It is a neutral, lipid soluble compound that can easily pass the blood brain barrier and other membranes in the body.[6] The urogenital system is divided functionally into two different embryologically component parts: the urinary system and the genital system which develops from the intermediate mesoderm derived from the dorsal body wall of the embryo. In mammals through the intrauterine life the intermediate mesoderm give rise to three developmental stages of kidney: pronephros, mesonephros and metanephros.[7] Pronephrose is the vestigial and earliest stage of nephric development in human, and resemble the mature functional structure of the lower vertebrate. It's originated early at the beginning of the fourth week around of human gestation and composed of 7-10 pairs of tubules in cervical region.[8,9] Mesonephrone is a principle transient excretory organ that functions only during embryonic development of human gestation while in large fish and amphibian considered as mature kidney.[8]

Metanephros is a functional, permanent and definitive phase of the nephric system development in amniotes; two functional tissue components are formed the permanent kidney the metanephric mesenchyme (blastema), which give rise the excretory system, and metanephric diverticulum (uretric bud) which give rise the collecting system.[9] Metanephric kidney development commences as a result of inductive interaction between the caudal end of the nephric duct which form an outgrowth called (ureteric bud) and metanephric mesenchyme (blastema).[10]

MATERIAL AND METHODS

Animal care and breeding

The study is performed on the Albino Rat (*Rattus rattus*). Healthy males and females were obtained from the animal housed of High Institute of Infertility Diagnosis and Assisted Reproduction Technologies/Al-Nahrain University. The ages ranged between [6-8] weeks and weight between (150-200gm). The rats are maintenance in the room at temperature 21 ± 4 °C with photoperiods 12hrs.Light /12hrs.Dark and the care is taking from sterilized and cleaned the cages. The dry food pellets and water were provide ad libitum[11]; the sexually mature females were isolated in the estrus phase which detected by making vaginal smears for each sexually mature female rat in the morning daily. Mating can be perform by placed one sexually mature male with one sexually mature female in breeding cage and kept overnight. In the morning of the next day, vaginal smears were taken and females were considered mated if the vaginal plugs and/or sperms were observed in the smears.[12] The day at which evidence of mating was observed defined as gestation day zero of pregnancy[13]; then the females transport for another cages without males.

Experimental design & treatment

20 healthy pregnant female rats were divided into two groups equally, Group I served as control group administrated distal water, and

Group II used as experimental group administrated carbamazepine drug as oral suspension formulation 100mg/5ml at dose 20mg/kg/rat daily via gastric gavage the dosing started from gestational day 1 and continuo until day 7 after birth in both group.

Histological preparations

On 7th day after birth, the kidneys of newborns were removed and washed by normal saline then the weight of the newborns and kidneys were measured, then fixed in Bouin's solution for [6-8] hours, dehydrated in ascending grades of ethanol alcohol (70%, 90%, 100%), cleared in xylene and infiltrated with filtered paraffin. The paraffin blocks were made and 5µm thin sections were obtained using a rotary microtome. The sections were stained with (H&E) and (PAS) stain; then sections were examined under light microscope [14] at magnification 10X, 40X, 100X.

Scanning electron microscope

Moreover, the sections were examined under the scanning electron microscope this can be achieved firstly, by fixation the specimen in glutaraldehyde fixative after that, the specimen is dried on filter paper and mounted on a metallic holder by using a double sticky tape, the specimen is coated by a thin layer of conductive metal (gold) and inserted into the

scanning electron microscope model AIS300C in the College of Education for Pure Science/Ibn Al-Haitham, Baghdad University.

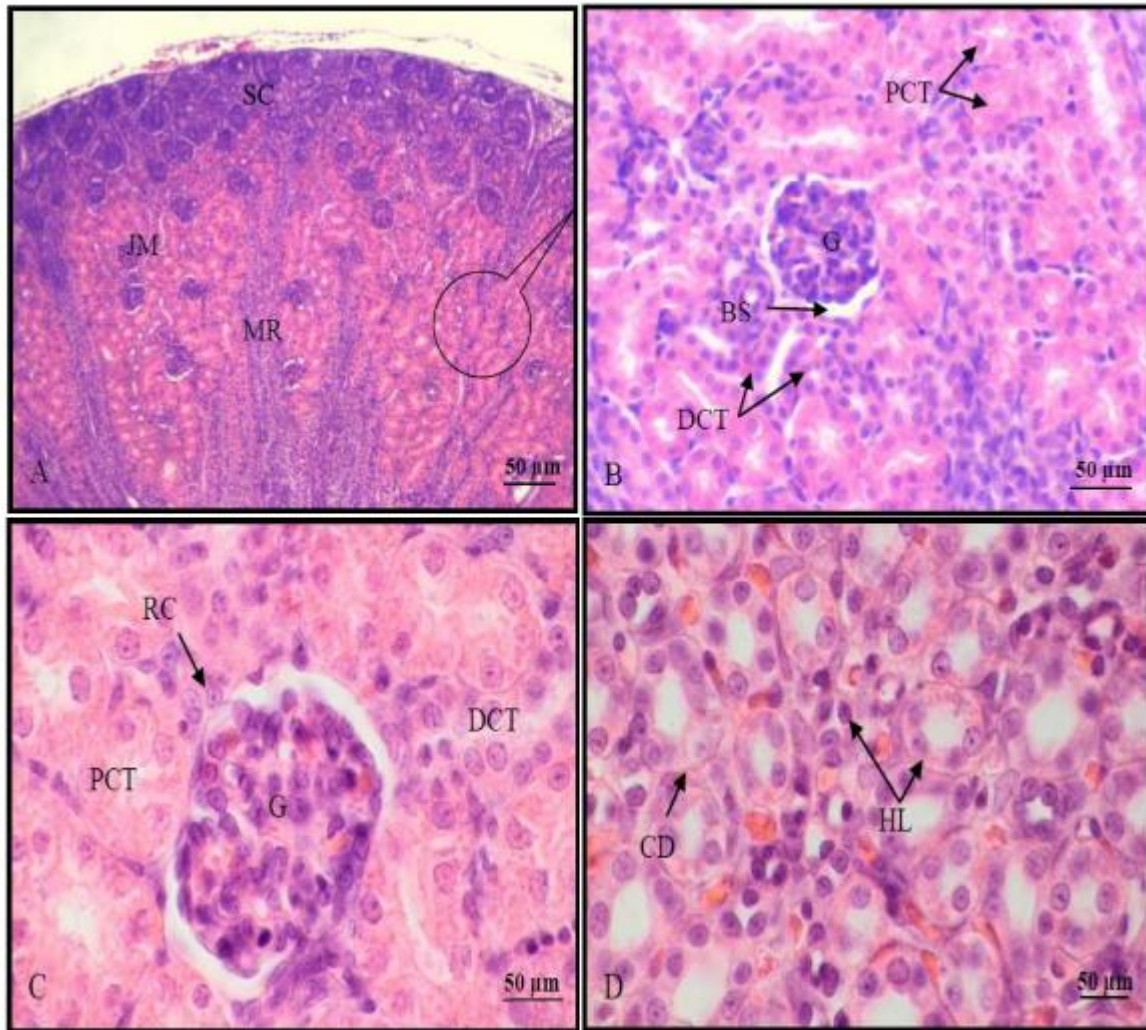
Morphometric parameter

The image analysis program is used to measure the diameter of renal corpuscles, glomerular tuft and Bowman's space in corticomedullary area at magnification 40X and also measure the diameter of proximal and distal convoluted tubules at magnification 100X.

RESULTS

At age 7 days old, the weight of newborns in control group was (11.355±0.645) while in treated group was (9.785±0.983); the weight of the kidneys in treated group was (0.0683±0.005) that compared to the weight in control group (0.0719±0.005); however there are no significant differences found in the weight of newborns and kidneys. The histological study using the light microscope observed that the kidneys of newborns in the control group showed the renal cortex and renal medulla, the renal cortex was occupied predominantly by later stages of developing glomerulus with a large number of the mature glomerulus appearance and the renal medulla, proximal convoluted tubules and distal convoluted tubules appearance (Fig.1).

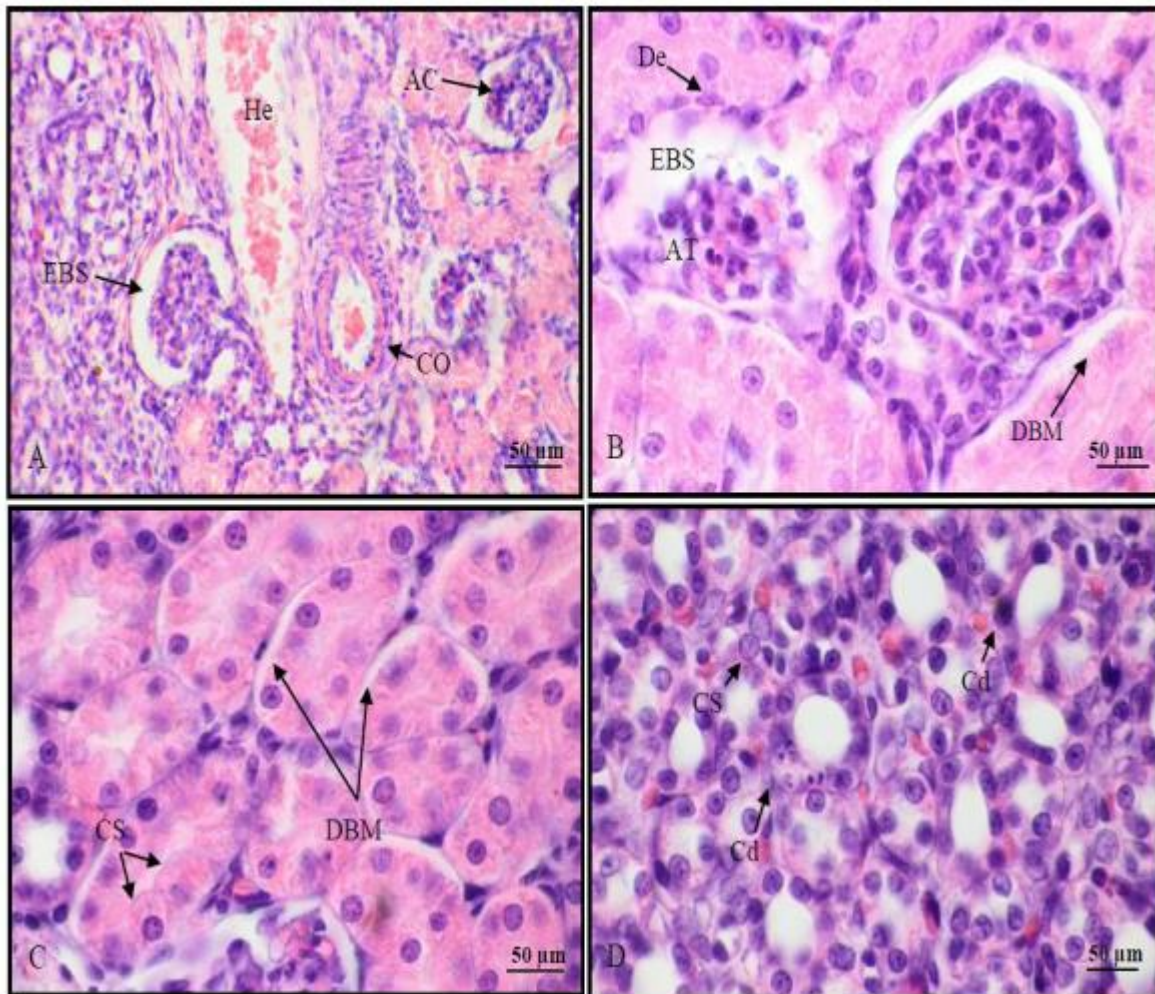
Figure1: Cross section of kidney in Albino Rat newborn at age 7 days of control group A 10X: normal histological appearance of kidney show the tow cortical region sub- capsular zone (SC), juxtamedullary zone (JM) and the medullary rays (MR) appear extending between the two zones, B 40X: The renal cortex of newborn kidney showed normal glomerulus (G) surrounded by Bowman's capsule which is formed of two layers separated by urinary space (US), proximal convoluted tubules (PCT) and distal convoluted tubules also appear, C100X: show the renal corpuscle (RC) surrounded by proximal convoluted tubules (PCT) and distal convoluted tubules (DCT), D100X: renal medulla (M) of newborn kidney showed collecting ducts (CD) and Henle's loops (HL))H&E).



While in the treated group showed obvious histological changes of the newborns kidneys treated with carbamazepine drug at dose 20mg/kg daily in cortical region which appeared in the form of an expansion of Bowman's space, atrophy of glomeruli, degeneration of partial layer of Bowman's

capsule, glomerular accumulation cells, hemorrhage, congestion and detach of tubular epithelial lining cells from basement membrane while in renal medulla showed degeneration of renal tubules and collecting ducts represented by (cell death, loss nucleus, and cell swelling) (Fig.2).

Figure2: Cross section of kidney in Albino Rat newborn at age 7 days of treated group with carbamazepine drug at dose 20mg/kg A 40X: show expansion of bowman space (EBS), glomerular cells accumulation (AC), Hemorrhage (He) and congestion (Co), B,C 100X: show glomerular atrophy (AT), expansion of bowman space (EBS), degeneration of partial layer of bowman capsule (De), detached of epithelial lining from basement membrane (DBM) and cell swelling (CS), D 100X: renal medulla (M) of newborn kidney showed cell death (CD) and cell swelling (CS) (H&E).



The renal cortex of the treated group showed strong Periodic acid Schiff reaction (PAS) in renal glomeruli as well as brush borders of renal tubules, the main histopathological changes appeared in the form of glomerular atrophy, expansion of Bowman's space,

degeneration and hypertrophy of partial layer of Bowman's capsule, glomerular cells accumulation, detach of tubular epithelial lining cells from basement membrane and degeneration of renal tubules (fig.3).

Figure3: Cross section of kidney in Albino Rat newborn at age 7 day of treated group with carbamazepine drug at dose 20mg/kg A&B 40X: show expansion of bowman space (EBS), glomerular atrophy (AT), glomerular cells accumulation (AC), hypertrophy of simple squamous epithelial lining cells of partial layer of bowman capsule (HY), C&D 100X: show expansion of bowman space (EBS), degeneration of partial layer of bowman capsule (De), detach of tubular epithelial lining cells from basement membrane (DBM), tubular degeneration (De) and brush borders emerge (Bb), (PAS).

The newborns kidneys under the normal and treated conditions was studied by scanning electron microscopy, the results appeared that the images of renal structures revealed by SEM in control group have demonstrated that a glomerulus (G) consists of complex network of blood capillaries which are usually covered by podocytes (P) with foot processes that give off

small finger-like projections, known as pedicels, while in treated group the scanning electron microscopic observations indicate that carbamazepine drug at dose 20mg/kg induced alterations of the kidney as previous results but more obvious such as expansion of Bowman's space, degeneration of partial layer of bowman's capsule and hypertrophy of

podocyte cells. In treated group the statistical analysis results found that the diameter of podocyte cells was increased in treated group

(9.619 ± 1.205) compare with control group (4.072 ± 0.225) with significant difference ($p < 0.001$) (Fig.4,5,8).

Figure4: Photographs of scanning electron microscope of Albino Rat newborn kidney at age 7 days of control group show the renal corpuscle (RC) consists of network of blood capillaries is glomerulus (G) which are usually covered by podocytes (P).

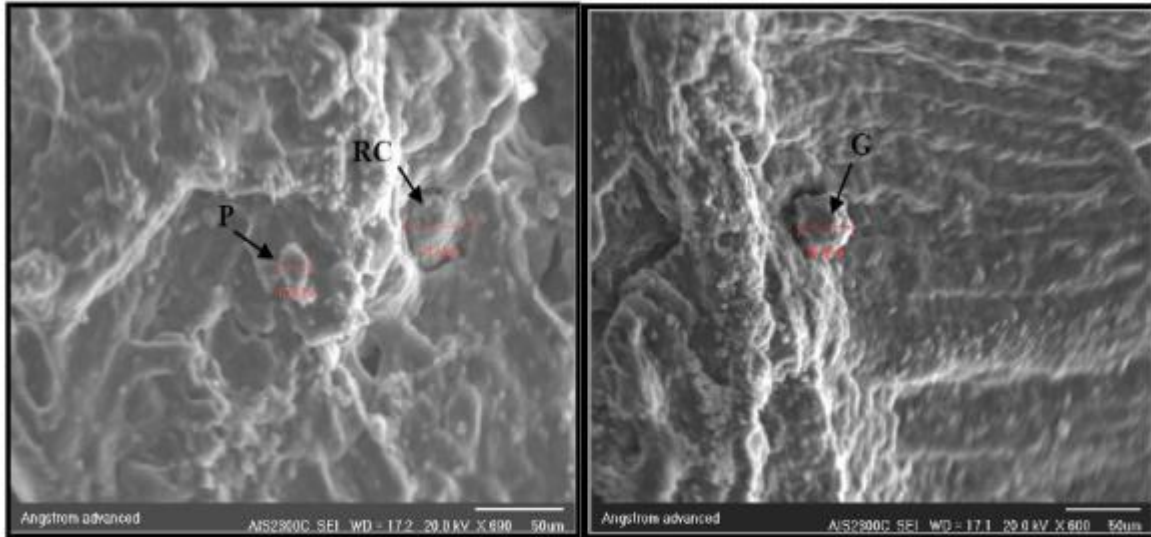
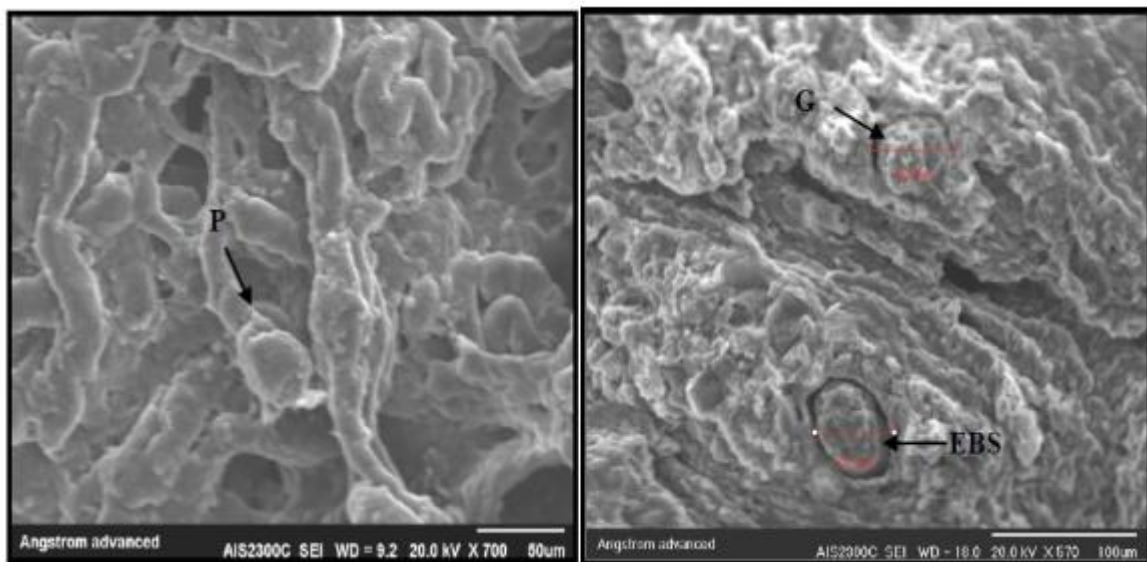


Figure5: Photographs of scanning electron microscope of Albino Rat newborn kidney at age 7 days of treated group with carbamazepine drug at dose 20mg/kg show expansion of Bowman's space (EBS) and hypertrophy of podocyte cells (PC).



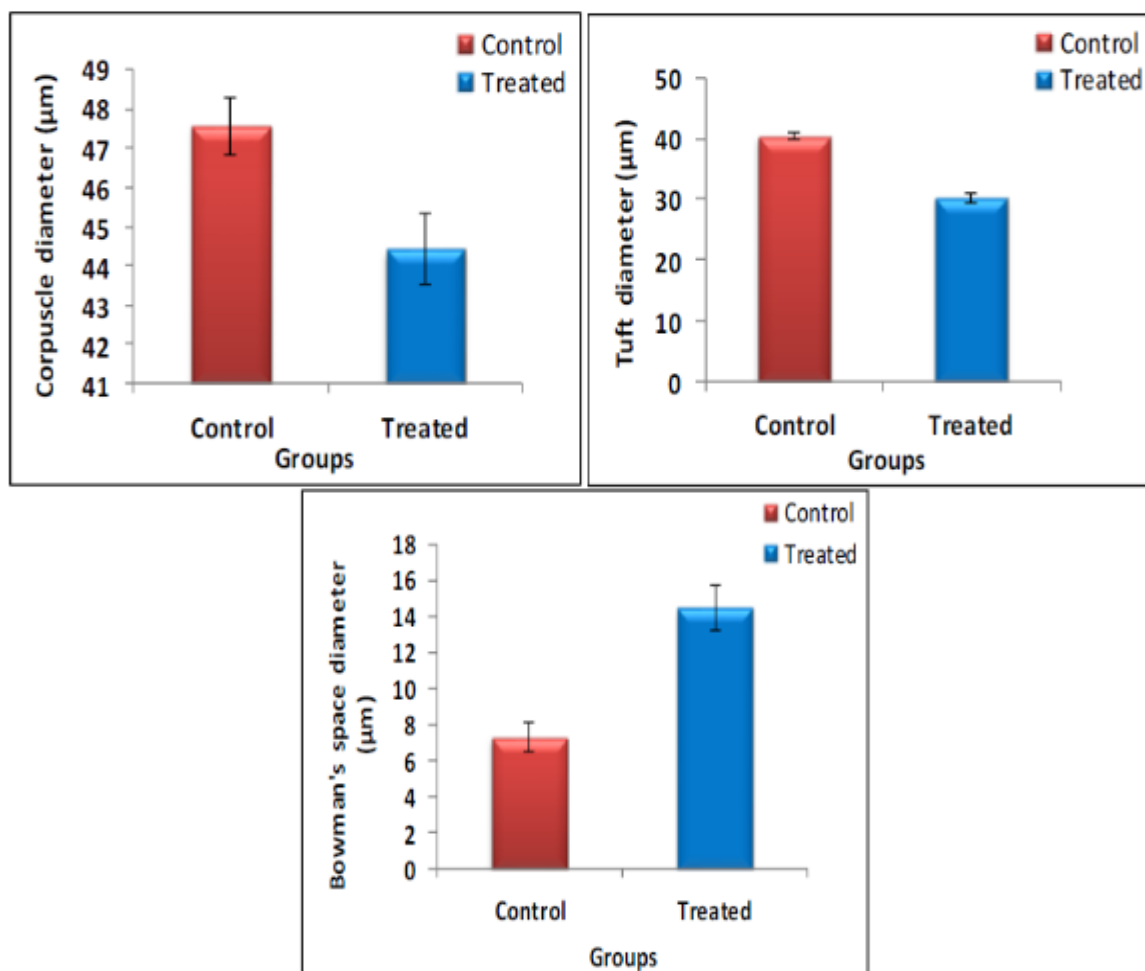
Statistical analysis

The statistical analysis results for the present study observed that the diameter of renal corpuscles, glomerular tuft and Bowman's space (measured at magnification 40X) in treated group was a statistically significant in comparison to control group ($p < 0.001$) (Table-1) and (Figure-6).

Table: 1 Comparison of renal corpuscle, glomerular tuft and Bowman's space between the treated and control groups.

Day	Glomeruli diameter (µm) (Mean ± S.E.)					
	Corpuscle		Tuft		Bowman's space	
Day 7	Control group	Treated group	Control group	Treated group	Control group	Treated group
	47.57±0.7	44.435±0.894*	40.322±0.588	30.249±0.681*	7.247±0.815	14.456±0.1242*

Figure 6: Show the effect of carbamazepine drug at dose (20mg/kg/day) in the mean diameter of renal corpuscle, glomerular tuft and Bowman's space of Albino Rat newborns at age 7 day

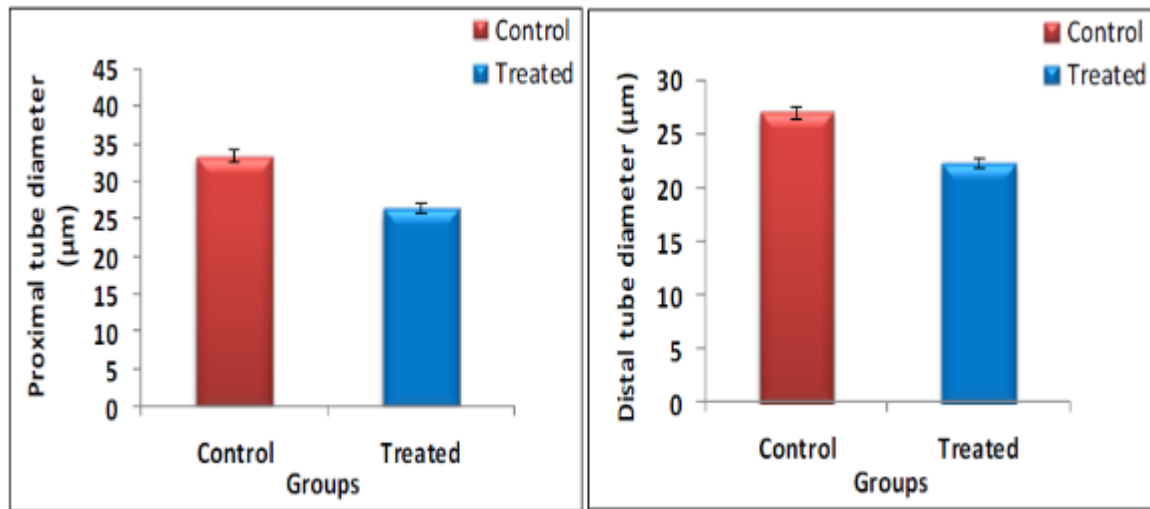


While the statistical analysis results found that the diameter of renal tubules proximal and distal convoluted tubules (measured at magnification 100X) in treated group was statistically significant in comparison to control group ($p < 0.001$) (Table-2) (Figure-7).

Table: 2 Comparison of proximal and distal convoluted tubules between the treated and control groups.

Day	Tubes diameter (µm) (Mean ± S.E.)			
	Proximal convoluted tubules		Distal convoluted Tubules	
Day 7	Control group	Treated group	Control group	Treated group
	26.911±0.524	22.203±0.514*	33.264±0.841	26.369±0.627*

Figure8: Show the effect of carbamazepine drug at dose (20mg/kg/day) in the mean diameter of podocyte cells of Albino Rat newborns at age 7 day



DISCUSSION

Carbamazepine is a first generation of antiepileptic drugs. It has been approved for the treatment of partial and generalized tonic-clonic seizures (grand mal) with or without secondary generalization, trigeminal neuralgia and as a second-line for treatment bipolar disorder.[15] The developmental toxicity which is caused by environmental insult such as drugs is a structural or functional alteration, reversible or irreversible, which interferes with normal growth, differentiation and development.[16]

The newborns kidneys were appeared affected in all animals treated with carbamazepine drug; the main histopathological defects as following: expansion of Bowman's space which characterized by enlargement of Bowman's space and these results is an agreement with.[17] that observed may be either due to glomerular shrinkage or atrophy as a result of glomerular cell death or inflammations of glomerular epithelial cells leading to glomerular cell death. In addition, this result is an agreement with.[18] that suggested the enlargement of Bowman's space may be due to hydrostatic pressure which increased within Bowman's capsule due to glomerular hyper-filtration or as a consequence of shrinkage of the capillary tufts due to atrophy.

Glomerular atrophy, this result is an agreement with.[18] may be due to chronic degenerative changes in the glomeruli and subsequent hemodynamic alterations leading to shrinkage and contraction of one or more glomerular capillary tufts, generally correspond with enlargement of Bowman's space. These results are also consistent with.[19] and[20] confirmed that the atrophy of glomeruli and degeneration of renal tubules leads to retard renal growth.

Congestion and hemorrhage appeared in the kidneys of newborns between the epithelial lining of renal tubules, collecting ducts and between the glomerular cells; this may be due to drug toxicity leading to death of epithelial lining cells in tubules and glomerulus. This result confirm the findings of previous researches[21] that mentioned the congestion is a consequence of acute inflammation leading to blood flow changes inside the vessels and occur relax and extend of blood vessels then leading to accumulation of blood inside vessels. Also,[22] found that the congestion caused due to the concentration of the drug in critical sits of the cells, which leads to higher levels of red blood serum than do simple plasma drug levels.

Another effect is detached of epithelial lining cells from the basement membrane of renal tubules and collecting ducts may be due to the toxicity of drug and this result is an agreement

with[23] that found detached the epithelial lining from the basement membrane resulting to death of tubules epithelial lining cells and this may due to destruction of the cells consequence of loss cytoskeleton and destruction of plasma membrane.

Hypertrophy appeared in the epithelial cells lining the renal tubules and simple squamous epithelium of partial layer of Bowman's capsule; this result is an agreement with[24] that reported the hypertrophy is an increase in the size of cells resulting to increase in the size of the organ and this enlarged occur by increasing the amount of structural proteins and organelles caused either by increasing the functional demand or by specific hormonal stimulation. Also, accordance with[25] who mentioned that the renal epithelial cells hypertrophy can occur by cell cycle-dependent or -independent mechanisms, the cell cycle-independent hypertrophy probably include the inhibition of pH sensitive lysosomal enzymes, leading to decrease protein degradation, and consequently an increase in cell protein content and cell hypertrophy.

Degeneration is appeared in the glomeruli and epithelial lining cells of tubules and collecting ducts and also simple squamous epithelium of Bowman's capsule represented by loss nucleus, cell swelling and may be resulting to cell death. This result is an agreement with[26] that observed the cell death resulting from exposure to endogenous metabolites, environmental and dietary carcinogens, some anti-inflammatory drugs, and genotoxic cancer therapeutics consequence to DNA damage and then cell death. Additionally,[27] reported that the glomerular cells degeneration may be due to glomeruli inflammation leading to renal failure, while[28] reported that the inflammation activates many renal cell types to produce cytokines, which directly damage renal cells and intensify inflammation.

Accumulation is appeared in glomerular cells may be consequence of glomerular cell death was leading to shrinkage of glomeruli; this result is an agreement with[29] that reported

the accumulation of the cells result to disappearance of cells either due to loss nucleus or accumulation of extracellular matrix gradually, leading to loss of glomerular cell.

In the present study, there are several changes in the diameter of renal corpuscle, glomerular tuft, Bowman's space, proximal and distal convoluted tubules in the newborns at age 7 days treated with carbamazepine drug at dose 20mg/kg daily with significant differences ($p < 0.001$) between control and treated group. The diameter of renal corpuscle, glomerular tuft and Bowman's space in control group about (47.57 ± 0.7), (40.322 ± 0.588) and (7.247 ± 0.815) consecutively, while in treated group (44.435 ± 0.894), (30.249 ± 0.681) and (14.456 ± 0.242) consecutively, this may be due to the drug accumulation in the proliferation glomerular cells. The renal corpuscle in treated group appears decrease in mean diameter compare with control group this result is an agreement with.[30] While the Bowman's space appear dilated compared with control group this result is an agreement with.[31]

Also the mean diameter of renal tubules in the present study discovered that the carbamazepine drug can modulate the developing newborns kidney with significant differences between control and treated group. The diameter of proximal and distal convoluted tubules in control group was (26.911 ± 0.524) and (33.264 ± 0.841) consecutively, while in treated group was (22.203 ± 0.514) and (26.369 ± 0.627) consecutively. This may be due to the cell death consequence of drug toxicity.

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