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PROTECTIVE EFFECT OF L-CARNITINE ON GLYCEROL- INDUCED RENAL TOXICITY IN ADULT MALE ALBINO RAT (LIGHT AND ELECTRON MICROSCOPIC STUDY)

By

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ABSTRACT

Background: Muscle injury (rhabdomyolysis) resulting from traumatic causes as traffic accidents and from non traumatic causes as hyperthermia, muscle ischemia and exposure to different renal toxic agents is one of the causes of acute renal failure (ARF). L-Carnitine, is an anti-oxidant used as a safe and effective nutritional supplement, is effective in preventing renal injury.

Objective: To elucidate the possible effect of L-Carnitine on glycerol-induced acute renal toxicity or failure.

Material and Methods: Sixty adult male albino rats were divided into three equal groups: Rats in group 1 served as a control and were given daily saline by intraperitonial (i.p.) injection for one week, those in groups 2 were injected with glycerol (10 mL/kg, i.m.).Concomitant with and 24 h after glycerol injection, L-Carnitine (200 mg/kg, i.p.) was administered to group 3. The specimens were prepared and stained routinely with hematoxylin and eosin for general morphological and structural study, and processed to obtain ultrathin sections which were stained and examined by transmission electron microscope (TEM).

Results: Histopathological findings in group 2 rats confirmed that there was renal impairment by cast formation and tubular degeneration and necrosis. All these factors significantly improved by L-Carnitine supplementation.

Conclusion: L-Carnitine, possibly via its antioxidant properties, ameliorated glycerol-induced myoglobinuric kidney injury. In this model, the protective effect of L-Carnitine treatment may provide a new insight into the treatment of rhabdomyolysis-related ARF.

INTRODUCTION

The most common model of myoglobinuric ARF in vivo is produced by intramuscular injection of hypertonic glycerol which causes myolysis, hemolysis and intravascular volume depletion, and exposes the kidney to a large burden of heme proteins, myoglobin and hemoglobin. It has been suggested that heme proteins or their degradation products (including hematin and iron) display tubular nephrotoxic properties, partially mediated by the generation of free oxygen radicals ***(Baligaet al., 1999).***

L-Carnitine is an anti-oxidant used successfully in the treatment of a variety of diseases. The protective effect of L-Carnitine on kidney tissue has been proved in various models such as cisplatin-induced injury of the kidney and

small intestine, gentamycin-induced nephrotoxicity, ischemia–reperfusion injury of the kidney and chronic renal failure. L-Carnitine can also act as a chelator by decreasing the concentration of cytosolic iron which plays a very important role in free radical chemistry ***(Rebouche & Seim 1998 and Salsoso et al., 2014).*** For this reason, the aim of this study was to throw a light on histological and ultra-structural changes of the kidney under the effect of one of exogenous anti-oxidant substance (L-Carnitine) supplementation in glycerol-induced acute renal toxicity or ARF.

MATERIALS AND METHODS

Sixty adult male albino rats of local strain with body weight ranged from 200-250 gm were used in this study. Animals were divided into three equal groups:

Group I: Control group was given daily saline intraperitonial for one week ***(Rebouche and Seim, 1998).***

Group II: Acute renal toxicity (glycerol) group was injected with glycerol (10 mL/kg, i.m.) daily divided on both limbs for five days ***(Zager, 2000, Aydogdu et al., 2006 and Ustundag et al., 2009).***

Group III: Glycerol and L-Carnitine-treated group was concomitant withL-Carnitine (200 mg/kg, i.p.) and extended for 48 hours after glycerol injection. All i.m. injection volumes were divided equally into two and were injected into each hind limb ***(Zager, 2000, Aydogdu et al., 2006 and Ustundag et al., 2009).*** After anesthesia by light ether, abdomen was opened and the two kidneys of each rat were obtained, sliced sagittally/axially and divided into two equal specimens; one was processed for light, and the other for electron microscopic examination.

1. Specimens were processed for light microscopic examinations and were fixed in 10% formalin for 24 hours. Paraffin sections (5 um thick) were prepared and stained with hematoxylin and eosin for general morphological and structural study.

2. Specimens for electron microscopy were processed as follows:

Small fragments from the renal cortex were fixed in a mixture of 2.5% gluteraldehyde and 2.5% paraformaldehyde in 0.1ml cacodylatebufferat pH 7.4 for at least 3 hours at room temperature. The fixed tissues were rinsed several times in cacodylate buffer, postfixed in 1% osmium tetroxide, dehydrated in ascending grades of alcohol to be lastly embedded in Eponresin. Ultrathin sections of 60 nm thicknesses each were cut with glass knife, stained with 2% uranyl acetate and lead citrate and examined under transmission electron microscope ***(Hayat, 1989).***

RESULTS

Control group: The renal cortex of the control group appeared with normal structure. It contained the renal corpuscles, proximal convoluted tubules (PCTs), distal convoluted tubules (DCTs) and collecting tubules ***(fig.1)***, together with the interstitial tissue. Also,electron microscopic examination showed normal components of the glomerular filtration barrier and podocytes ***(fig.2,3)*** as well as PCTs, DCTs and collecting tubules ***(fig.4,5&6)***.

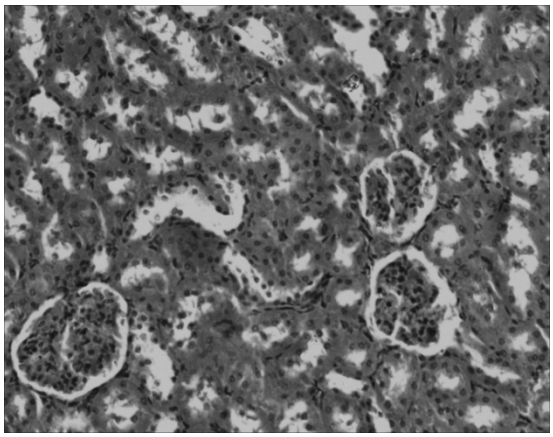

Figure (1): Photomicrograph of renal cortex in adult albino rat (control group) showing normal histological structure of the different parts of the kidney. ***(HX. &E 200x)***

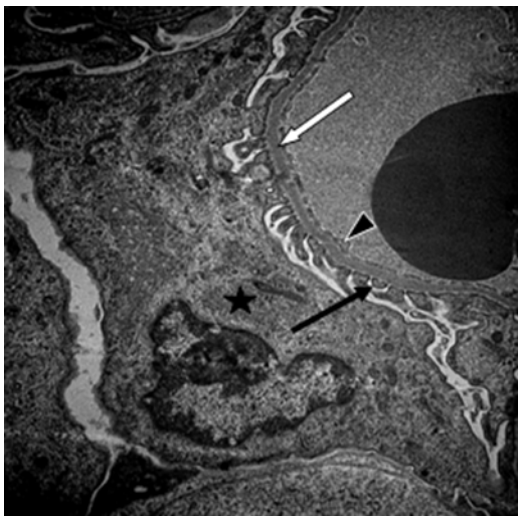

Figure (2): Electron micrograph in kidney of adult albino rat (control group) showing the component of the glomerular filtration barrier including the fenestrated capillary endothelium (▲), glomerular basement membrane (⇦), podocyte feet processes as well as the nucleus of the podocyte (➡). Notice the filtration slits between the secondary processes of podocyte cell (★). (15000 x)

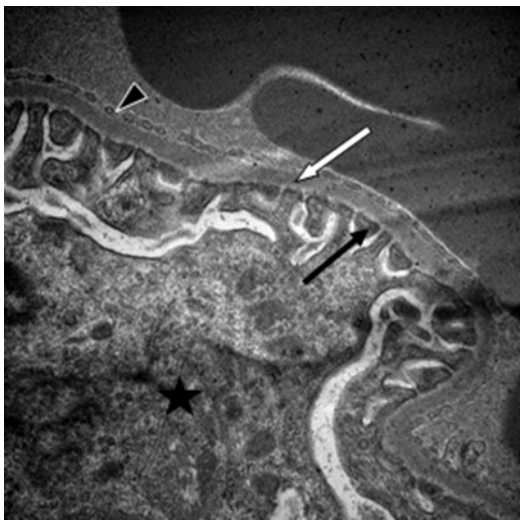

Figure (3): Electron micrograph of the previous field with higher magnification with higher magnification showing more details of the structure of the glomerular filtration barrier including the fenestrated capillaryendothelium (▲), glomerular basement membrane with its trilaminer appearance(⇦), podocytecell (★). Notice the filtration slits between the secondary processes of podocyte cell (➡).
(25000 x)

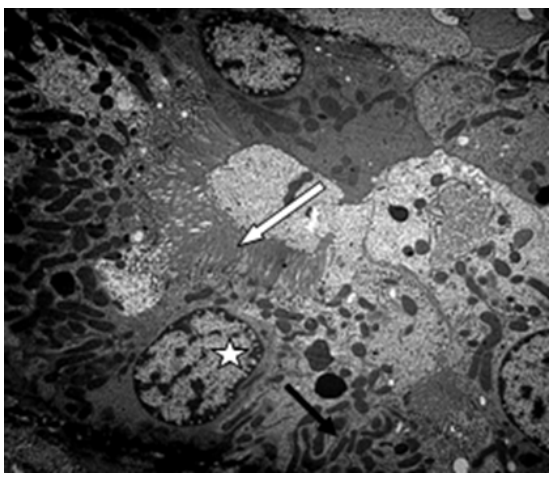

Figure (4): Electron micrograph of PCT of control group showing PCT cells with well developed microvilli constituting the brush borders (⇦), normal central round nucleus (☆), and normal distribution of cytoplasmic organelles (➡).
(5000x)

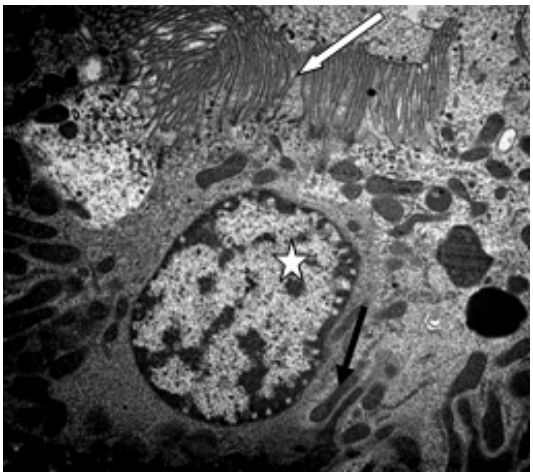

Figure (5): Electron micrograph of the previous field with higher magnification showing PCT cells with well developed microvilli (⇦), normal central round nucleus with normal chromatin content (☆), and normal distribution of mitochondria (➡). (10000 x)

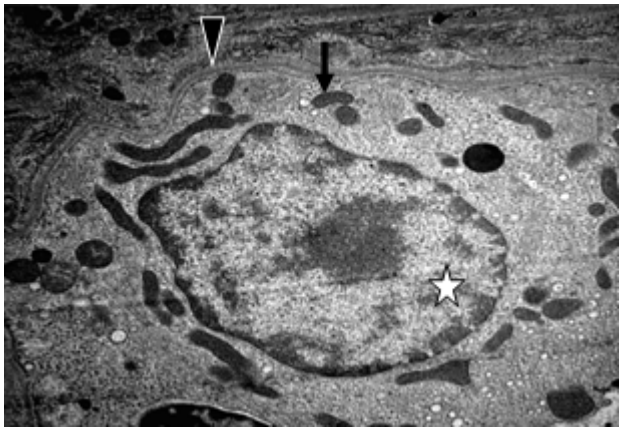

Figure (6): Electron micrograph of DCT of control group showing DCT cell with its central round nucleus (☆) normal distribution of mitochondria (⬇), and normal cell membrane with its trilaminer structure (▼) (12000 x)

Acute renal toxicity (glycerol) group: The renal corpuscles appeared markedly small with glomeruli showing different degrees of degeneration in the form of shrinking, and widened capsular spaces. Some glomerulia wereruptured or even atrophied and necrotic. The parietal layer of Bowman's capsule appeared partially lined by low cubical epithelial cells with oval nuclei.

PCTs and DCTs in the affected areas appeared with wide lumina. Most of the lining cells appeared flattened, detached apical cytoplasm, and most cells contained pyknotic nuclei. Some other cells showed swollen, fragmented or even karyolitic nuclei. The tubules contained in their lumens granular basophilic and homogenous acidophilic casts ***(fig. 7)***. The interstitium showed intense mononuclear cellular infiltration and areas of hemorrhage were also noticed in the affected parts ***(fig.8 & 9)***. Ultrastructure examination of the glomerular capillary are showed continuous endothelium with no fenestrations, and thick homogenous filtration membranes ***(fig.10)***.

PCTs and DCTs showed flattened cells with basal small atrophied electron dense nuclei, destruction of cytoplasmic organelles, with intracellular vaculation, destruction of microvilli, thickening and distortion of basement membrane ***(fig. 11)***.

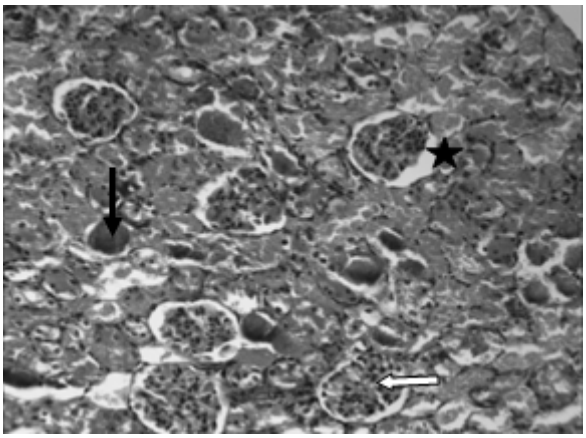

Figure (7): Photomicrograph of renal cortex in adult albino rat (glycerol group) showing shrunked glomerular tuft with wide subcapsular space (★) as well glomerular lobulation (⇦) the lumen of some renal tubules are occupied with glomerular basophilic casts (⬇).Most of the lining cells show pyknosis.
(HX.&E 200x)

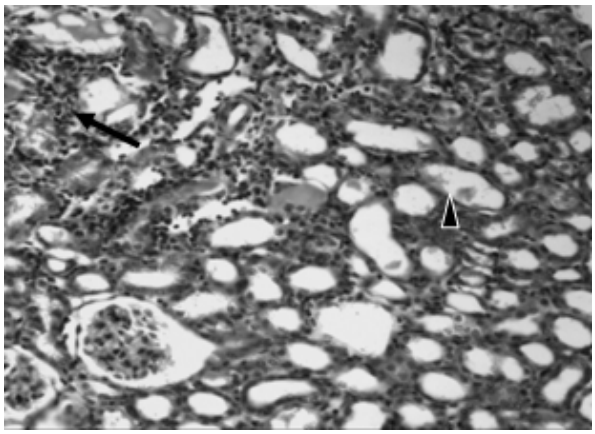

Figure (8): Photomicrograph of renal cortex in adult albino rat (glycerol group) showing wide flattened renal tubules lined by low cubical cells containing pyknotic nuclei (▲), together with increased mononuclear inflammatory cells infiltration (⬅).
(HX.&E200x)

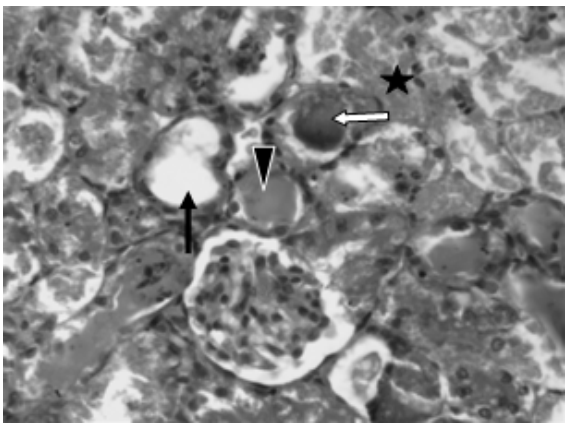

Figure (9): Photomicrograph of renal cortex in adult albino rat (glycerol group) showing wide renal tubules lined by thin degenerated low cubical cells containing pyknotic nuclei (⬆) some tubules are completely occupied by homogenous acidophilic hyaline casts (▼) others are occupied by basophilic glomerular casts (⇦) together with massive degeneration of renal interstitial tissues (★). (HX.&E 400x)

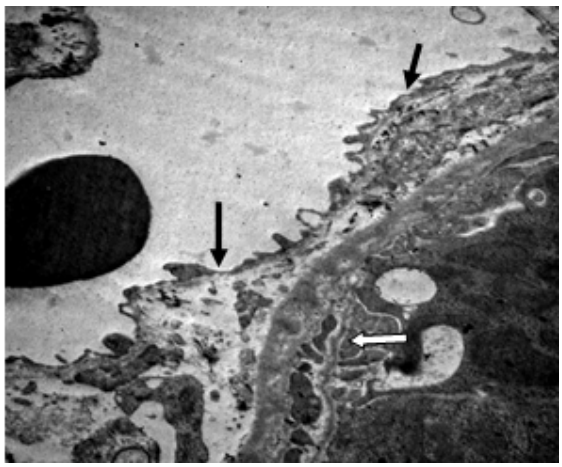

Figure (10): P Electron micrograph in kidney of adult albino rat (glycerol group)showing flattened and degenerated glomerular capillary with no fenestrations (⇦). Notice affected podocyte with its degenerated feet processes (⬆) (15000 x)

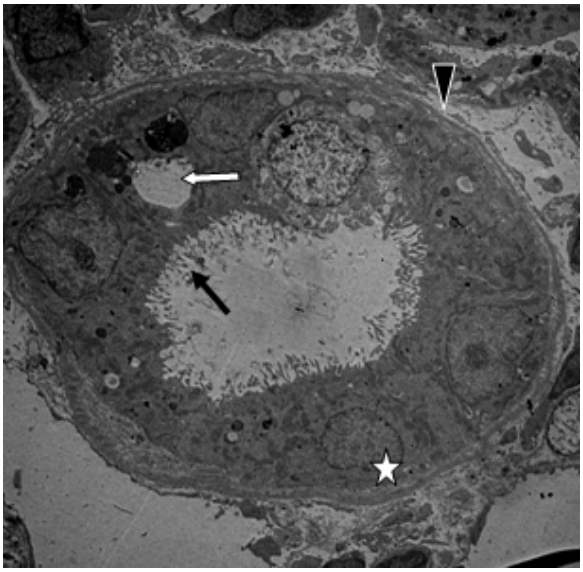

Figure (11): P Electron micrograph of PCT of glycerol group showing flattened cells with basal condensed nuclei (☆), intracellular vaculation (⇦), destruction ofmicrovilli (⬅), thickening and distortion of basement membranes (▼). (4000 x)

Glycerol and L-Carnitine-treated group: There was a remarkable improvement in the general histological structure of the different parts of uriniferous tubules and interstitial tissue of the kidney, with decrease in the number of the casts and reduction in the mononuclear inflammatory cells infiltration than in glycerol group.

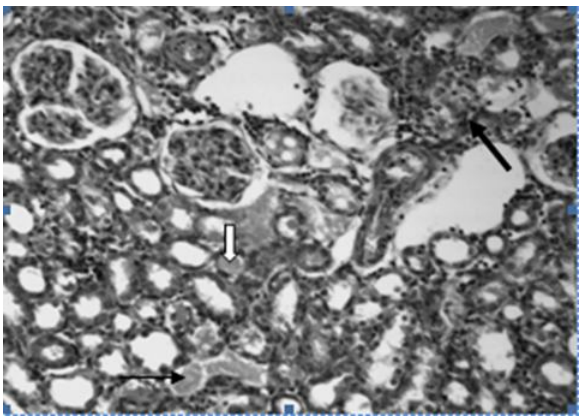

Figure (12): Photomicrograph of renal cortex in adult albino rat (treated group) showing certain improvement in the general histological structure of the kidney with decrease in the number of the casts (⇨), restriction of the hemorrhagic areas (⟶) and reduction in the mononuclear inflammatory cells infiltration than in glycerol group (↖). (HX. &E 200x)

The PCTs appeared with slightly widened lumina, slightly flattened than glycerol group and lined by low cubical cells, contained in their lumens only homogenous acidophilic cast and no granular basophilic cast. The DCTs appeared with wide lumina. The lining cells appeared less flattened with pale cytoplasm and detached apical cytoplasm but less than that of acute renal toxicity (glycerol) group ***(fig.12&13)***.

Ultrastructure changes showed improvement in the components of the glomerular filtration barrier where the capillary endothelium regainedits fenestrations, glomerular basement membrane structure, as well podocyte cells with their processes and filtration slits appeared between secondary processes ***(fig.14)***.

PCTs showed less flattened cells than glycerol group, with normal microvilli. There were intracytoplasmic lysosomes containing dense bodies, together with minimal intracellular vaculation, less splitting and thickening of basement membrane ***(fig.15&16)***.

DCTs cells showed mild destruction of cytoplasmic organelles, and mild intracellular vaculation ***(fig.17)***.

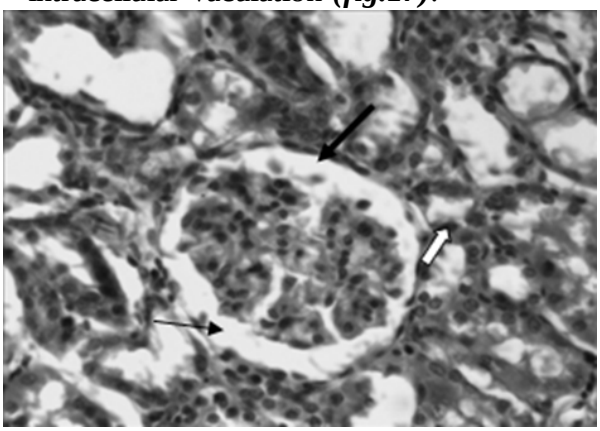

Figure (13): Photomicrograph of renal cortex in adult albino rat (treated group) showing different parts of the uriniferous tubule with almost normal histological structure. Notice normal renal corpuscle, with normal glomerulus (⬇), clear subcapsuler space (⟶), the PCTs have narrow lumina and lined by pyramidal cells (⇩). (HX. &E 400x)

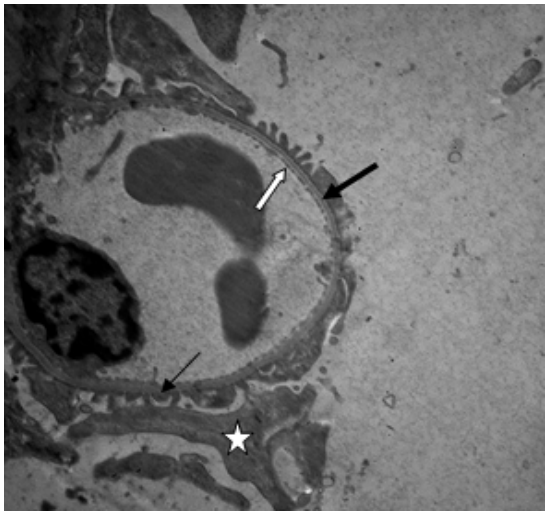

Figure (14): Electron micrograph in kidney of treated group showing improvement in the component of the glomerular filtration barrier than in glycerol group, where the capillary endothelium regain its fenestration (⇨), glomerular basement membrane appear with itstrilaminer structure (⬅) as well podocyte cell with their primary and secondary processes (☆). Filtration slits appear also between secondary processes (⟵).
(10000 x)

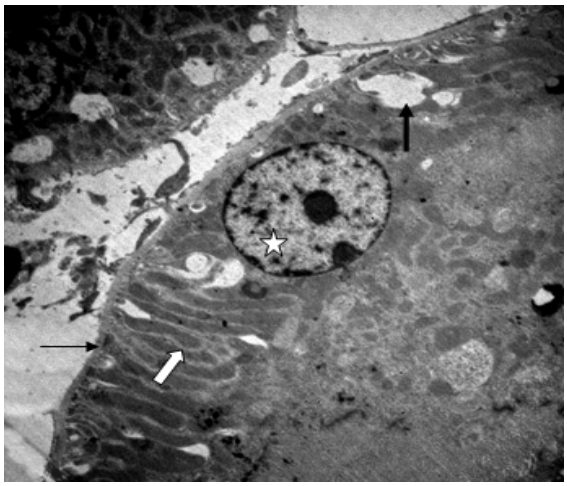

Figure (15): Electron micrograph of PCT of treated group showing the presence of basal round nucleus (☆) improved thin basement membrane (⟶) and almost normal mitochondria longitudinally oriented in the basal invaginations of the cell (⇧) there are still minimal intracytoplasmic vacuoles (⬆).
(10000 x)

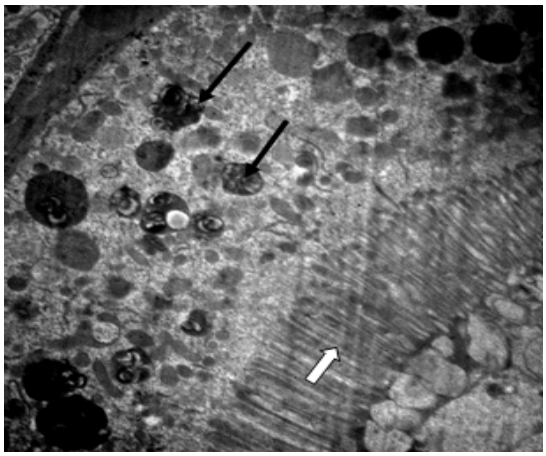

Figure (16): Electron micrograph of PCT of treated group showing less flattened cells with normal microvilli (⇨).Notice the presence of many lysosomes containing electrondensebodies (➡).
(10000 x)

Figure (17): Electron micrograph of DCT of treated group showing improvement in the ultra structure in the form of slight irregular shaped nucleus of almost normal size (☆), minimal destruction of cytoplasmic organelles (⟶), basement membrane with minimal splitting and decreased thickness (⇦). Notice the presence of minimal intracytoplasmic vaculation (⬅).
(12000 x)

DISCUSSION

The occurrence of acute renal failure (ARF) following untreated rhabdomyolysis has been put at between 17 and 33% of cases and accounts for between 3 and 15% of all cases of ARF. Iron, O_2 free radicals and myoglobin play a critical role in the pathogenesis of glycerol-induced

myoglobinuricARF ***(Beetham, 2000 and Sharma et al., 2012).***

In acute renal toxicity (glycerol) group, some of the affected renal corpuscles appeared markedly small with shrunken glomerular tuft and wide subcapsuler space. Some of the corpuscles showed completely destroyed glomerular tuft. This was due to ischemic, as well as toxic, renal insults induced by hemeproteins ***(Baligaet al., 1999).***

Byelectron microscope (EM) the glomerular capillary showed continuous endothelium with no fenestrations. The parietal layer of affected Bowman's capsule appeared partially lined by low cubical epithelial cells with oval to rounded nuclei. Thickening of the capillary wall is a result of widening of the subendothelial space by abnormal basement membrane material, and the formation of a new layer(s) of basal lamina. ***(Ivanyi et al., 2001 and Ivanyi et al., 2003).***

The PCTs in the glycerol group appeared with wide luminalined by thin degenerated low cubical cells containing pyknotic nuclei. Most of the lining cells appeared flattened with detached apical cytoplasm. The tubules contained in their lumens granular basophilic casts due to high content of iron and myoglobin pigments. These findings were similar to those of previous studies performed using the same model ***(Beetham, 2000.)***

In the present study, most of the affected cells of the uriniferous tubules revealed darkly stained shrunkenpyknotic nuclei. This could be explained by the fact that cell injurydue to induced glycerol toxicity, could cause breaking down of deoxyribonucleic acid (DNA) by endonuclease enzymes into short oligonucleotide fragments. The phosphoric acid groups become exposed for binding to the basic dye (hematoxilin) thus stained more deeply by the dyesand this in agreement with ***(Walter &Israel, 1987 and Singh et al., 2011).***

By EM, the PCTs in acute renal toxicity group showed flattened cells with destruction of cytoplasmic organelles, intracellular vaculation, destruction of microvilli, splitting and thickening of basement membrane and electron dense nuclei which lost their normal vesicular configuration. This could be considered as an early change in nuclear pyknosis ***(Chadially, 1982 and MC Gee et al., 1992).*** By EM, the DCTs showed cells with destruction of cytoplasmic organelles, intracellular vaculation, splitting and thickening of basement membrane and irregular shaped nucleus ***(Kalaiselvi and Panneerselvam, 1998)***.

The intracytoplasmic toxicity in the present work both at the light and ultra-structural level could be explained by interference with cellular aerobic respiration due to toxic cell injury, this lead to disturbance in the oxidative phosphorylation in the mitochondria and suppression of ATP production. This, in turn would led to failure of ATP dependent sodium pump at the cell membrane and in turn will result in accumulation of sodium intracellulary and consequent entry of water into the different cellular compartments ***(Cotron et al., 1994).***

The interstitium in the glycerol- induced renal tissue toxicity showed intense mononuclear cellular infiltration. This affection might be secondary to renal

cellular degeneration and necrosis. Areas of hemorrhage are met with in the renal interstitium due to advanced degeneration and destruction of some glomerular tuft of capillaries ***(Crawford, 1994).***

The histopathological findings in glycerol groups were due to rhabdomyolysis-induced renal injury, where renal hypoperfusion-ischemia, iron mediated proximal tubular cytotoxicity and cast formation were postulated to play interrelated mechanisms which led to proximal tubular necrosis and ARF. This may be explained by the fact that oxygen free radicals are capable of reversibly or irreversibly damaging compounds of all biochemical classes including nucleic acids, proteins, free amino acids, lipids, lipoproteins, carbohydrates and connective tissue macromolecules. This oxidative potential is counter-acted by effective intracellular antioxidant molecules ***(Warren et al., 2007).***

The iron catalyzes the free radicals reaction which is associated with lipid peroxidation and renal injury ***(Larbi, 1998).*** This change can alter membrane permeability, impair function of membrane proteins and enzymes, in addition lipid peroxidase have direct toxicity to cells and organelles.

If large amounts of myoglobin were released, the tubular reabsorptive capacity was exceeded, producing marked myohemoglobinuria and intraluminal free iron release with granular cast formation ***(Larbi, 1998)***. This may explain the presence of granular basophilic casts met with in H&E resulted in glycerol groups in our study.

It has been shown that myoglobin itself can exhibit peroxidase-like enzyme activity that leads to uncontrolled oxidation of biomolecules, lipid peroxidation, and the generation of cytotoxic effect ***(Warren et al.,2007).***

The critical molecular targets of heme iron-induced oxidant stress remain largely unknown. Evidence has been presented that lipid DNA, and protein oxidation may all be involved ***(Zager, 2000).***

Thickened basement membrane of the parietal layer of Bowman's capsule, and basement membrane of the tubules met with in our finding maybe explained by ***Farquhar and Palad (1964)*** who after study with electron microscopy, suggested that severe renal ischemiaca using the thickening of basement membranes are related to increased plasma proteins and abnormal exudates. This exudates stimulate the proliferation of mesangial cells which secret a fibrillar materials as well as mucopolysaccharides. This provide slittleinter cellular substance which helps to support capillaries. That agreed with ***Vergas et al. (1970)*** who stated that injured capillary wall lead to abnormal cell metabolism with leakage of plasma proteins through the wall of capillaries.

The present study was in agreement with ***Beetham (2000)*** who stated that glycerol treatment caused severe ARF, a marked renal oxidative stress. Histopathological findings confirmed that there was renal impairment by cast formation and tubular necrosis and a marked increase in iron accumulation in the tubular epithelium.

In treated (glycerol and L-Carnitine) group, there was certain improvement in the general histological structure of the different parts of the uriniferous tubules

and interstitial tissue of the kidney, with decrease in the number of the casts, and reduction in the mononuclear inflammatory cells infiltration than in glycerol group.

By EM, the glomerular capillary showed continuous endothelium with no fenestrations. This was in agreement with ***Kalaiselvi and Panneerselvam (1998).***

By LM, the PCTs of treatedgroup appeared lined by low cubical cells and less cells contained pyknotic nuclei. The PCTs contained in their lumens only minimal homogenous acidophilic cast and no granular basophilic cast. This was in agreement with ***Beetham (2000) and Sener et al. (2004)***.

By EM, the PCTs have normal microvilli and there were lysosomes containing dense bodies with minimal intracellular vaculation, minimal splitting and thickening of basement membrane. The DCTs of treated group appeared with wide lumina. Some of the lining cells appeared less flattened than that of acute renal toxicity (glycerol) group. By EMthe DCT cells of treated group rats showed, mild destruction of cytoplasmic organelles and mild intracellular vaculation ***(Sener et al., 2004)***. The interstitium showed reduction in the mononuclear inflammatory cells infiltration than in glycerol group.

The improvement in the general histological structure in kidney of treated group may be due to the fact that L-Carnitine supplementation enhances the activities of anti-oxidant enzymes such as catalase (CAT) and glutathione peroxidase (GPx) levels in kidney tissues ***(Kalaiselvi and Panneerselvam, 1998).*** L-Carnitine can also act as a chelator by decreasing the concentration of cytosolic iron, which plays a very important role in free radical chemistry ***(Mori et al., 2003,Zambrano et al., 2013 and Zambrano et al., 2014).***

L-Carnitine treatment enhanced nitric oxide (NO) levels significantly, most probably from endothelial cells, and this increase may lead to a reduction in the intensity of the ischemia in the kidney tissue ***(Arslan et al., 2003,Michael, 2008andSharmaet al., 2013).***

CONCLUSION

L-Carnitine improved the general histological structure of the kidney and produced a significant reduction in tubular degeneration, necrosis and cast formation in kidney exposed to toxic agents. So, this drug can be used as a protective drug especially with cases of renal failure.

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خلفية البحث: قد يؤدى تمزق العضلات الناتج عن أسباب رضية كحوادث السيارات أو أسباب غير رضية كنقص إمداد العضلات بالأكسجين إلى فشل كلوى حاد، وأن (إل-كارنيتين) وهو أحد مضادات الأكسدة يستعمل كمكمل غذائى مؤثر فى منع حدوث إصابات الكلى.

الهدف من البحث :صممت هذه الدراسة التجريبية فى الفئران من أجل توضيح تأثير الفشل الكلوي المحدث تجريبيا بواسطة إعطاء الجليسرول وتأثير مضادات الأكسدة (مادة إل- كار نيتين) عليها.

مواد وطرق البحث: إستخدم في هذه الدراسة ستون فأرا من الذكور البيضاء البالغة ، وكانت أوزانهم تتراوح ما بين 200 إلى 250 جراما وقد تضمنت مجموعات التجارب المجموعة الضابطة التى إشتملت على عشرين فأرا أعطيت محلول ملحى عن طريق الحقن في التجويف البريتوني لمدة سبعة أيام، ومجموعة الفشل الكلوي الحاد التى إشتملت على عشرين فأرا وقد أعطيت مادة الجليسرول عن طريق الحقن في العضل لمدة خمسة أيام، و المجموعة المعالجة التى إشتملت على عشرين فأرا أعطيت مادة الجليسرول عن طريق الحقن في العضل وذلك لمدة خمسة أيام ومعها مادة إل- كار نيتين عن طريق الحقن في التجويف البريتوني لمدة سبعة أيام.وقد تم فحص النسيج الكلوي لكل المجموعات بواسطة الميكروسكوب الضوئي مستخدما بعض الصبغات وهى الهيماتوكسلين والإيوسين بالإضافة إلى فحص النسيج الكلوي بواسطة الميكروسكوب الإلكترونى النافذ.

النتائج :وجود تغيرات نسيجية وخلوية عديدة وواضحة في الكلية نتيجة تمزق العضلات بواسطة إعطاء الجليسرول، وهذه التغيرات تتمثل فيتفصص وإنكماش في الكريات الكلوية أو حتى تمزق كامل لبعض هذه الكبيبات وتنخرها، وأيضا حدوث زيادة في حجم الخلايا المبطنة للطبقة الجدارية لغشاء بومان المحيط بالكريات الكلوية مع إتساع الفراغ بين الطبقة الجدارية والطبقة الحشوية لغشاء بومان. وعلي مستوي الميكروسكوب الإلكترونى حدث زيادة في سمك جدار الترشيح الكلويو إختفاء الثقوب في جدار الخلايا المبطنة لجدار الشعيرات الدموية المكونة للكريات الكلوية، أما الأنابيب الملتوية العلوية و السفلية فقد حدث إضمحلال وتنخر في الخلايا المبطنة لتلك الأنابيب مع وجود إتساع في تجويف تلك الأنابيب وإحتوائها علي نوعين من الإسطوانات الحبيبية وغير الحبيبية إلي جانب ظهور مساحات من النزيف وإرتشاح للخلايا الإلتهابية، وأيضا علي مستوي الميكروسكوب الإلكترونى حدث اضمحلال وتنخر في الخلايا المبطنة لكل من الأنابيب الملتوية العلوية والسفلية وحدوث تضخم وزيادة في الحبيبات الخيطية في خلايا تلك الأنابيب مع حدوث تنخر في معظم عضيات تلك الخلايا.

الإستنتاج: يقل حدوث التغيرات النسيجية والخلوية في الكلية نتيجة تمزق العضلات بواسطة إعطاء الجليسرول عند إستخدام أحد مضادات الأكسدة وهو مادة (إل- كار نيتين).