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Research Article

ACUTE RENAL FAILURE DUE TO RHABDOMYOLYSIS TREATED WITH OLMESARTAN

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ABSTRACT

Background: Myoglobinuric acute renal failure induced by glycerol injection is characterized by ischemic injury, vascular congestion, and the appearance of reactive oxygen metabolites. This is the first study to examine the role of Olmesartan in attenuating glycerol-induced rhabdomyolysis was examined. Methods: Male Wistar rats were deprived of water for 24 hours; then given intramuscular glycerol injections intramuscularly with 10 mL/kg body weight of 50 % glycerol for group 2 and 3. Rats in group 3 were treated for 6 consecutive days with Olmesartan 3 mg/kg body weight. An hour after the last dose, a blood samples were collected so that renal function could be assessed. Then the rats were sacrificed to get kidneys, one for histological investigations, and the other for enzyme assays. Results: A significant increase in the levels of urea and creatinine, and a significant decrease in the activity of reduced glutathione was detected in glycerol-induced rats; these markers were reversed upon Olmesartan treatment. The biochemical data were supported by evaluation with kidney histopathology. All these effects induced by glycerol were attenuated upon treatment with Olmesartan. Olmesartan treatment has improved all the studied marks that induced by glycerol. Conclusion: these findings suggest that Olmesartan can significantly diminish kidney damage by glycerol.

Keywords: Glycerol; Olmesartan; Rats; Rhabdomyolysis.

INTRODUCTION

Acute kidney injury (AKI) is a worldwide critical clinical common problem, with a high mortality rate[1]. Rhabdomyolysis is one of the important reasons of community-acquired AKI. Rhabdomyolysis-induced AKI (RIAKI) is a systemic syndrome produced by the collapse of damaged skeletal muscle and which release its contents (i.e., myoglobin, sarcoplasmic proteins and electrolytes) into the plasma, that filtered through the glomeruli, that is leading to acute kidney injury (AKI) via different mechanisms, such as intratubular obstruction secondary to protein precipitation, renal vasoconstriction, inflammation, and tubular damage associated with reactive oxygen species (ROS) production. Renal accumulation of myoglobin and, heme derivations produced these harmful effects[2].

All components of the renin angiotensin aldosterone system, that has an important role in the cardiovascular system, are present in the kidneys[3]. Renin is present in principal cells of connected tubule (CNT) cells, and, of cortical and medullary collecting ducts of normal rat kidneys. Chronically raised intrarenal angiotensin II (ANG II) levels exert a stimulatory action on proximal tubule angiotensinogen (AGT) transcript and, protein, which is mediated by the AT1 receptor. AGT contribute to intratubular ANG I and, ANG II formation in distal nephrons[4].

Renal vasoconstriction associated with rhabdomyolysis is related to the activation of the renin-angiotensin aldosterone system (RAAS), which is induced by volume depletion secondary to fluid sequestration within the damaged muscle. Also the imbalance between vasoconstrictors and, vasodilator products that regulate renal blood flow plays a role in the vasoconstriction[2]. Both receptors of angiotensin II type 1 (AT1) and, type 2 (AT2) receptors are expressed in adult human kidneys. AT2 receptors are mainly localized in the interlobular arteries[3], proximal tubules, collecting ducts, renal interstitial cells, arcuate arteries, afferent arterioles and outer medullary descending vasa recta[5]. These strategic renal locations suggest an involvement of the AT2 receptors in the regulation of renal hemodynamic and tubular functions[6]. In addition, AT1 receptors are expressed in the afferent and efferent arterioles, glomeruli and, proximal tubules. Almost all classical angiotensin II-induced functions, such as vasoconstriction, sodium and water reabsorption, as well as increased cellular hypertrophy, proliferation and extracellular matrix deposition in the kidney, are mediated by AT1 receptors. The renin-angiotensin blocker may have better Reno-protective effects than other antihypertensive classes, as Angiotensin receptor several clinical trials have shown[3]. Furthermore, angiotensin-converting enzyme inhibitors and, angiotensin receptor blockers (ARBs) found to delay the progression from microalbuminuria to macroalbuminuria in diabetic patients[7] and lessen the incidence of end-stage renal disease in patients with diabetic nephropathy[8]. Experimental and clinical studies with ARBs showed that AT1 receptors are involved in the development of renal disorders[3]. In addition, basic and clinical research supports the use of renin-angiotensin aldosterone system (RAAS) inhibitors in diabetic nephropathy[9].

This study was performed to explore the curative effect of Olmesartan in a rat typical of experimental AKI.

MATERIALS AND METHODS

Induction of AKI

All experiments were achieved on male Wistar rats weighing 250 - 300 g. They were modified for one week prior to the commencement of experimental procedures. The rats were fed

standard commercial rat pellets, permitted water *ad libitum*. They were reserved under controlled environmental conditions (temperature 23 ± 2°C, humidity 55 ± 15%, lighting regimen of 12-h light: 12-h dark). All methods in this study were performed in concordance with regulatory guidelines on the care and use of laboratory animals; National Research Council [NRC] 2011. Guide for the Care and Use of Laboratory Animals. 8thed. Washington: National Academies Press.

For renal morphological and functional studies, three groups, each containing 6 animals was used, and dehydrated 24 h prior to inducting acute tubular necrosis. The first group of rats (untreated, N) was given no injections; the second and third groups of rats were given intramuscular injections of 50 % (v/v in sterile water) glycerol (10 mL/kg, IM) in their hind limbs[10]. Followed 30 minutes, by oral gavage syringe, and daily in the next six days by an Olmesartan obtained from Sigma-Aldrich Co. LLC, (3 mg/kg/day, p.o)[9] suspended in sodium carboxymethyl cellulose solution (vehicle) (sodium CMC 0.5% w/v) for group (O), or vehicle for the group (GLY). Control group (N) was daily gavage with the oral vehicle (CMC) to ensure same handling conditions for all animals in the experiment.

After 6 days, an hour after the last dose, each rat was anesthetized with ether. A blood sample was captured from the heart for functional assessment. Kidneys were then extracted, one for histological investigations and the other for enzyme assays. Handling and treatment of animals was performed according to protocols set forth in the Guide for the Care and Use of Laboratory Animals.

Kidney Function Assessment

Blood samples were collected via heart puncture. Creatinine and urea concentrations were assayed to assess renal function.

Serum Creatinine Concentrations

Plasma creatinine concentrations were measured (CREA, Roche/Hitachi Modular p analyzer), which is based on a rate-blanked and compensated picric acid colorimetric assay.

In this enzymatic method, creatininase activity was used to convert creatinine to creatine. Creatinine, in alkaline solution, forms a yellow-orange complex with picrate. The absorbance of samples and standard were measured at 505 nm (after 30 and 90 seconds, respectively) by using (Hitachi U-1800).

Serum Urea Concentration

The urea was measured using the Roche/Hitachi Modular P Analyzer kit. The reaction depends on the combination of ammonia compounds with sodium salicylate and sodium hypochlorite, which are directly proportional to the urea concentration in the sample. The colored complex was measured by spectrophotometrically at 340 nm.

Reduced Glutathione determination

The nephrectomy was carried out directly. Reduced glutathione GSH was measured by Assay Kit (Abnova) in kidney tissue stored at -80◦C. GSH was measured spectrophotometrically according to the improved 5, 5'-dithiobis (2-nitrobrnzoic acid DTNB). This process combines deproteination and detection (reagent A) into one reagent. A yellow product is formed by the reaction of DTNB with reduced glutathione. The optical density of the product (measured at 412 nm) is directly proportional to glutathione concentration in the sample.

Macroscopic and Histological examination and grading

Kidneys obtained from all animals were capsulated, and sectioned longitudinally into two equally sized pieces, kidney sections appearance were examined macroscopically, then fixed in 15% paraformaldehyde solution for 24 hours. Specimen preparation was performed by dehydrating with graded ethanol, cleared in xylene, and then embedded in paraffin wax. 4-5 micrometer-thick serial sections were cut using a rotary ultra-microtome. Hematoxylin and eosin staining were used for histopathological examination using a light microscope with the camera connected to a computer for photographic documentation. Blind analysis was performed on the samples to determine the extent of kidney injury based on the technique described by Erdogan *et al*[11].

The examinations focused on grading the damage to the proximal kidney tubules, using the following parameters: tubular cell necrosis and apoptosis, cytoplasmic vacuole formation and tubular dilatation. Interstitial edema and medullary congestion were also assessed. The severity of these lesions was determined based on the percentage of involvement of the kidney. The renal glomerular injury, inflammation, and hyaline dystrophies were examined, where the presence of these injuries was grade (1); and their absence was grade (0). The mean score for each parameter was determined and subjected to statistical analysis.

Statistical analysis

Results were expressed as the mean ± one standard deviation (SD). The Graph Pad Prism (Version 6) statistical package was used to perform the Statistical analysis. For serum creatinine and urea concentration, parameter comparisons between the groups were performed using a one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test; $p < 0.0001$ statistical significance was adopted for the analysis. Lesion score and histological score (non-parametric values) were analyzed using the Mann Whitney U test, and the frequency of categorical binary data was evaluated using Fisher's exact test; statistical significance was set at $p < 0.05$.

RESULTS

Injecting 50 % of glycerol in water (10 ml per kg of body weight) into the muscle of both hind limbs has induced an acute renal failure. Within 2 hours after this injection, the urine was burgundy red in color due to the presence of heme pigments.

The Olmesartan Effects on Kidney Function

Creatinine and urea are two principal clusters of renal function variables.

Urea Serum Level

The urea and creatinine serum levels in (Gly) rats were higher significantly than those in (N) rats. The urea level was 32.68 ± 7.34 mmol/L in (N) rats; whereas the urea level reached 116.66 ± 22.15 mmol/L in the (Gly) rats. Administration of Olmesartan significantly reduced urea levels (80.66 ± 19.52 mmol/L) compared with that of (Gly) rats. As shown in Figure 1.

Creatinine Serum Level

The creatinine level was 0.38 ± 0.069 µmol/L, and 1.93 ± 0.217 µmol/L in (N) rats and (Gly) rats, respectively. In contrast, the creatinine levels were significantly reduced (1.011 ± 0.049 µmol/L) compared with (Gly) rats after administration of Olmesartan. As shown in Figure 1.

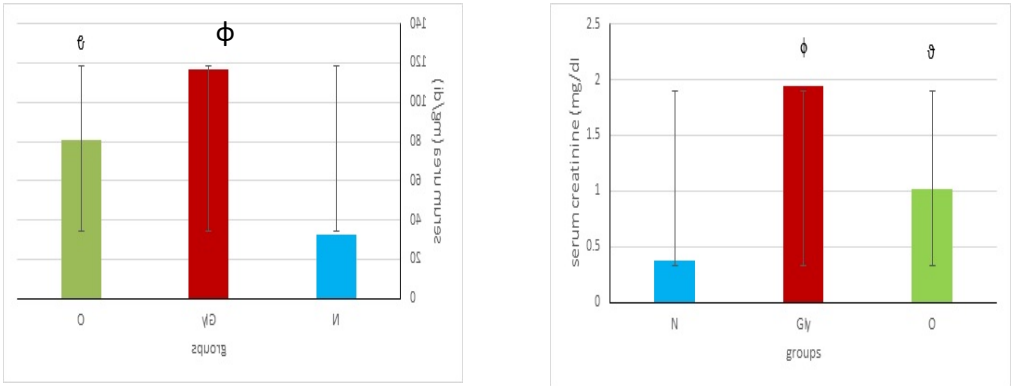


Figure 1: Serum urea and creatinine levels. φp < 0.0001 vs. N, ϑ p < 0.0001 vs. Gly

Olmesartan Effect on GSH activities in kidneys tissues

Reduction levels of GSH were found in (Gly) group (Figure 3). Data demonstrated that the levels of GSH in the (N) group are significantly higher than that of Gly-injected model rats. The administration of glycerol led to a reduction in GSH from 4.031 mmol/L to 2.7 mmol/L, compared with the (N) group. In contrast, O-treated rats that received glycerol showed the significant increase in GSH elevation (6.65 mmol/L vs 2.7 mmol/L, ϑ P < 0.0001), when compared with glycerol alone.

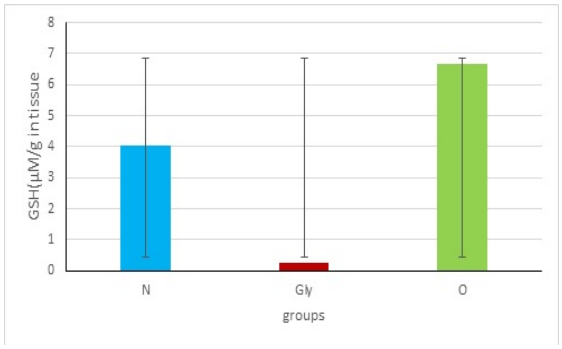
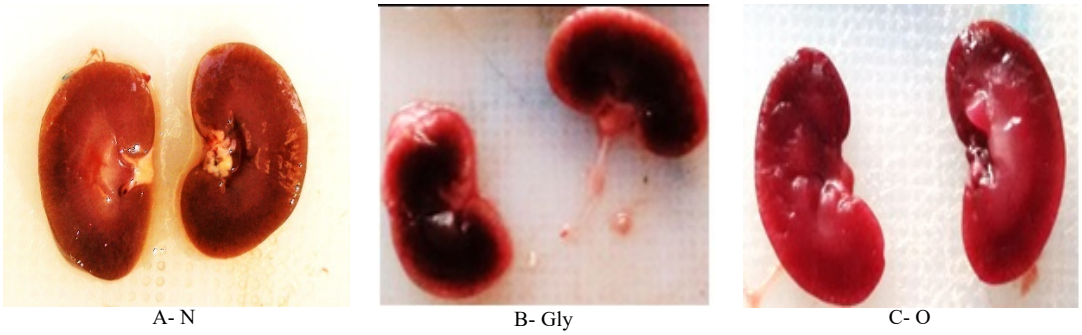


Figure 2: Effects of MSM on renal glutathione (GSH) content in glycerol-induced AKI. φp < 0.0001 vs. N, ϑ p < 0.0001 vs. Gly



A- N B- Gly C- O

Figure 3: Representative macroscopic kidney changes: (N) normal group; (Gly) glycerol group; (O) Olmesartan group

Macroscopic and Histological Results

Macroscopic Evaluation

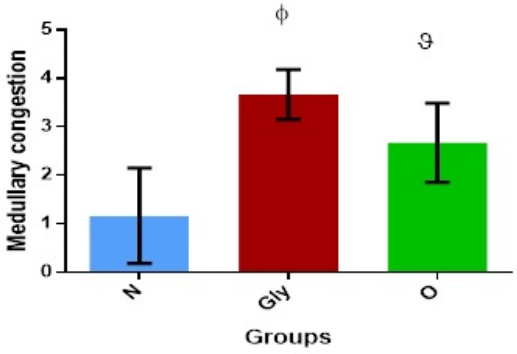
In control group (N) Kidneys had normal macroscopically appearance and color; the same was in the group (O). However, kidneys in the injured group (Gly) were bigger than those in the control group, with different macroscopic morphology. They revealed the yellow cortex with dark brown medulla. Noticed congestion and edema (Figure 3)

Histopathologic Evaluation

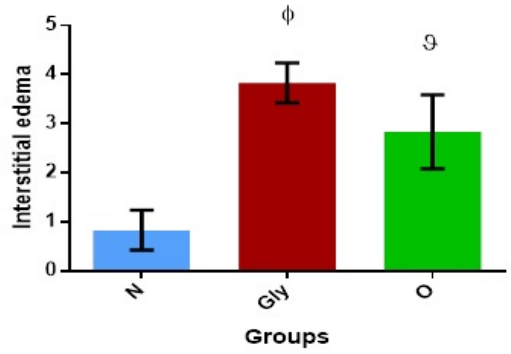
In histological specimens from glycerol-treated rats (Figure 4 B and C). Morphologic changes in proximal tubules in the subcapsular region of the renal cortex were registered primarily. Severe tubular necrosis and tubulorrhexis was observed in many of the proximal convoluted tubules. Swelling of mesangial spaces and mesangial cells in glomeruli was evident; however, many of them appeared to be normal. In the boundary zone between the cortex and medulla, the tubules were lined by epithelial cells with vacuolar and hydropic change. The lumen often contained granular material and exfoliated epithelial cells. Tubular epithelium was often attended, and some tubules were dilated and contained pigment casts. Only focal areas of necrosis were present in this region. In the interstitial, focal mononuclear infiltration was observed. Within inner medullary collecting duct, close to the papillary tip, the presence of pigment casts was a prominent finding. All these lesions were absent in the control group (Figure 4 A).

Renal tubular, medullary congestion and interstitial edema scores were significantly higher compared to control group (N), (P < 0.05). Hyaline dystrophies and glomerular injuries were also observed higher significantly compared to the control group (N), (P < 0.05).

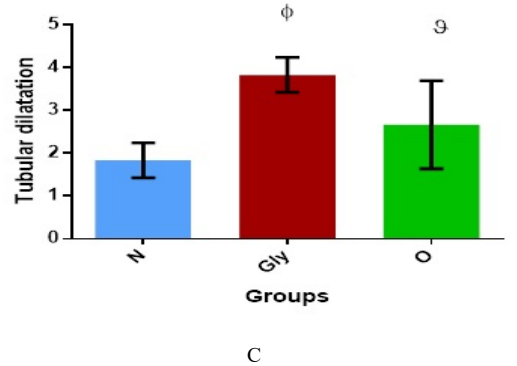
Histological alterations in specimens from the Olmesartan-treated groups were markedly reduced (Figure 4 D and E). The histological scores of these futures were significantly lower than of the injured group (Gly), ($P < 0.05$), as compared to the (Gly) group.



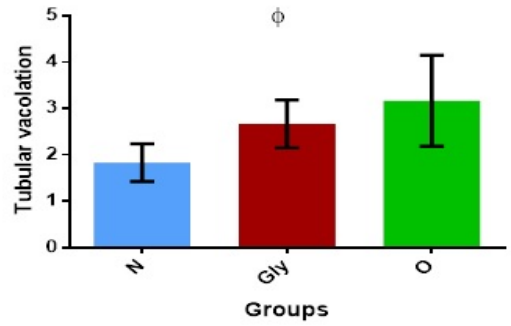
A
ϕ significant vs. N group P=0.0011<0.05; ϑsignificant vs. Gly group P=0.04<0.05



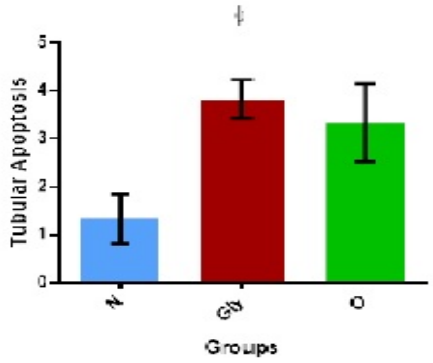
B
ϕ significant vs. N group P=0.0011<0.05; ϑsignificant vs. Gly group P=0.0271<0.05



C
ϕ significant vs. N group P=0.0011<0.05 ; ϑ significant vs. Gly group P<0.0303<0.05

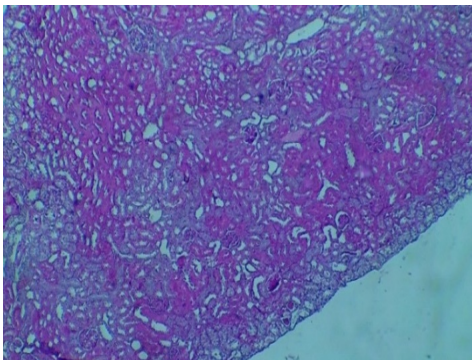


D
ϕ significant vs. N group P=0.0227<0.05

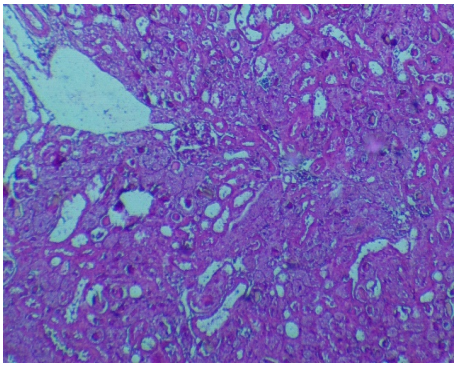


E
ϕ significant vs. N group P=0.0011<0.05

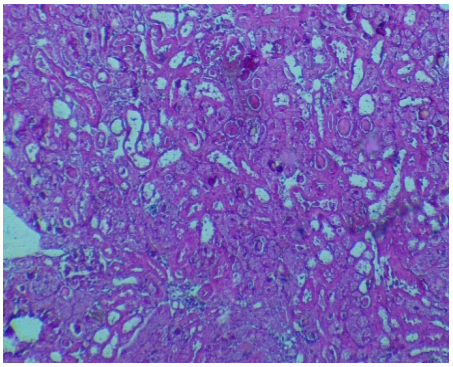
Figure 4: Effect of Olmesartan on the histological score of damage on tubular apoptosis; tubular vacuolation; tubular dilatation; interstitial edema; medullary congestion. Each column represented as the mean ± SD. N: control group, Gly: glycerol, O: Olmesartan



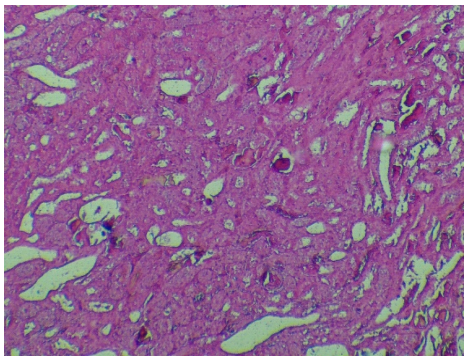
A- N x10



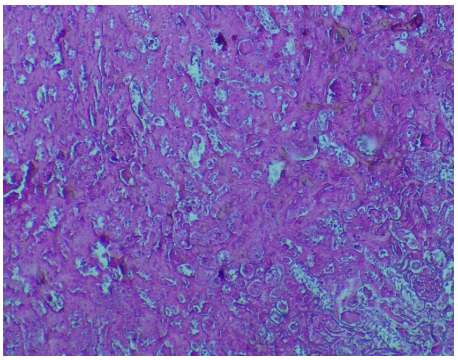
B- Gly1 x10



C- Gly2 x10



D- O1 x10



E- O2 x10

Figure 5: Representative histomorphological kidney changes: (N) normal group; (Gly) glycerine group; (O) Olmesartan group. All photomicrographs were taken at a magnification of 10x. A- (N) represent kidney section of a control rat showing normal architecture. B- (Gly) representkidney section of a glycerol treated rats showing glomerular deformation, tubular dilatation, vacuolation, swelling and degeneration of their lined epithelial cells, vascular congestion, and hyaline dystrophy. C-(O) represent kidney section of Olmesartan-treated rats showing the enhancement in tubular and glomerular injuries and other pathologic alterations, with some tubular filled with sick sediments

Table 1: Effects of Olmesartan on glomerular injury and hyaline dystrophy, expressed as a frequency of injured animals in each group.

feature	**Glomerular injury**			**Hyaline dystrophy**		
Groups	injury	No injury	Significance	injury	No injury	Significance
N	0	6		0	6	
Gly	5	1	§	6	0	ǁ
O	6	0		0	6	‡

§ P = 0.0076 < 0.05 as compared to N group; ǁ P = 0.0011 < 0.05 as compared to N group; ‡ P = 0.0011 < 0.05 as compared to Gly group.
N: control group; Gly: glycerol, O: Olmesartan

DISCUSSION

Hypertension is often accompanied by renal injury. This study investigates the effects of Olmesartan in a rhabdomyolysis-induced Acute renal failure (ARF) induced by glycerol.

An intramuscular administration of a single dose of glycerol is the most appropriate animal typical that clinically mimics the rhabdomyolysis-induced renal failure in humans[13]. The increased levels of urea and creatinine serum levels in this study demonstrate that the administration of glycerol induces a typical pattern of renal failure. Compared to (N) group the urea and creatinine serum levels was increased significantly in the (Gly) group by 257 % and 410 %, respectively. These findings are supported by Manikandan *et al*[14] and Kim *et al*[15].

The existent study examines the effects of Olmesartan on glycerol-induced ARF. Reiterated treatment with Olmesartan alleviates the increase in serum creatinine and urea concentration, marks of acute renal injury. They were reduced significantly to 31 % for urea and 48 % for creatinine in the group (O) compared with (Gly) rats.

To further investigate the antioxidant effects and reno-protective properties of Olmesartan, GSH was examined. The low activities of antioxidant enzymes in the renal cortex, along with the glycerol nephropathy, exacerbate the oxidative damage. The GSH level, compared with (N) rats, was significantly decreased 93 % in the (Gly) rats. Many studies such as Manikandan[15] and Rieger[17] have shown same results. In contrast, in the (O) rats compared with (Gly) rats, it increased significantly by 2364 %; thus, treating with Olmesartan significantly impaired glycerol-mediated increases of kidney GSH levels.

Serum creatinine and urea concentration were enhanced by repeated administration of (3 mg/kg/day) Olmesartan, which has demonstrated the reno-protective effect of Olmesartan, and facilitated the activity of antioxidant enzymes.

Abul-Ezz revealed that glutathione supplementation in rats resulted in partial protection from acute renal failure induced by glycerol[16]. The importance of GSH in the prevention and treatment of ARF was confirmed in this study. Increased intracellular GSH levels or the presence of GSH in tubular fluid, or both may explain the protective effect of GSH[17]. Glycerol may provoke renal lesions by many mechanisms including damage from free radicals, lipid peroxidation, iron accumulation in the kidney, antioxidant depletion, glomerular dysfunction, decreased NO levels and altered dysfunctional renal morphology[18].

Significant structural changes, including tubular dilation, vacuolation, necrosis accumulation of cellular debris, damaged glomerular structure, hemorrhagic and hyaline cast deposits, as well as apical blabbing in the kidneys of glycerol treated rats, were shown in our histopathological studies. Similar biochemical and histopathological changes following glycerol treatment have been registered as[15,19].

Myoglobin induced ARF may due to exacerbating intrarenal regional hypoxia and medullary vasoconstriction [20]. Renal ischemia and presence of myoglobinuria may play role in the increased severity of acute tubular necrosis[12]. The deterioration in kidney function represents the combined effects of cortical damage, medullary hypoxic injury and tubular obstruction. The presence of large numbers of distal nephron heme pigment casts have been observed in every myoglobinuric ARF study, including this one. Cast formation with marked dilation of the collecting ducts and focal tubular necrosis and rupture at the outer medullary region probably play a major role in the deterioration of kidney function[20]. This is a quite different finding from uranyl nitrate, mercuric chloride and gentamicin-induced ARF, exhibiting a direct nephrotoxic effect and producing a marked decrease of kidney ectopeptidase activity[21].

These changes were mild in the animals treated with Olmesartan (group O). Interestingly, Olmesartan treatment did not decrease the pathological variations in the kidney to the same extent as the variations in urea and serum creatinine concentrations. This result proposes that the drug performance maybe, in part, by recuperating the function of the remaining nephrons rather than averting direct renal injury caused by glycerol exposer.

While the exact mechanism of glycerol-induced renal injury remains somewhat unclear, it is believed that various cell-mediated immune responses and inflammatory mediators are involved in the pathophysiology of AKI[22].

AT2 receptors have been found to mediate the actions of angiotensin II by antagonizing the AT1 receptor effects in the vasculature. Blocking the angiotensin receptor AT1 receptors raise the angiotensin II levels, which could potentially induce signaling through AT2 receptors. AT2 receptor activation increases renal sodium and water excretion and influences renal blood flow via the formation of renal nitric oxide (NO) and cyclic GMP production[3]. NO plays a crucial role in regulating local blood flow and aqueous outflow in blood vessels. NO levels were upgraded in glycerol-induced renal failure group[14].

Scavenging the nitric oxide by myoglobin cause a vasoconstriction; so any agents capable of increasing nitric oxide were tested to prevent rhabdomyolysis-induced damage[2].

Progressive tissue injury is allied with an increase in intrarenal ANG II content, which improves oxidative stress, chronic pro inflammatory and proliferative responses.

Various growth factors, cytokines and lipid mediators are concerned in the pathogenesis of renal disease products of the cyclooxygenase (COX) and lipoxygenase (LO) pathways of arachidonate metabolism have a myriad of physiological and pathological effects in the kidney. ANG II can trigger the 12/15-LO, leukocyte-type presents in the kidney and COX pathways, the crops of which, in turn, can trigger p38 mitogen-activated protein kinase (MAPKs) and inflammatory genes. Therefore, chronic Angiotensin receptor Preventer (ARP) administration impedes glomerular injury and overturns up regulation of AT1R and several key inflammatory mediators in obese Zucker rats. ARB can decrease 12/15-LO and COX-2 expression, thus supporting the role of the Ang II–AT1R pathway in the regulation of these enzymes. Furthermore, this data exposes an additional mechanism of the reno-protective effects of ARBs in renal cortex of obese Zucker rat [23]. Also, treatment with ARB obstructs the increases in distal nephron renin mRNA and protein expression[4]. This is consistence with several studies that investigated the reno-protective effect of Olmesartan medoxomil 10 mg/kg/day in many models, such as doxorubicin-induced nephrotoxicity[24], or nephropathy resulting from hypertension alone or associated with diabetes[9]. Many other angiotensin receptor blockers (ARBs) (such as losartan, irbesartan, and candesartan) in clinical and pre-clinical studies exert similar reno-protective effects that are also not readily explained by reductions in blood pressure[23].

This study suggests that AT1 receptor blockade by Olmesartan may be an effective mechanism for the treatment of nephropathy.

CONCLUSION

The current study examined the influence of AT1 receptors on the curative effect of Olmesartan in representative renal failure. Olmesartan perform edreno-protective role against rhabdomyolysis induced by glycerol exposure.

The biochemical findings and the histopathological analysis demonstrated that administration the Olmesartan rescued the cells from glycerol-induced damage. It also resulted in an improvement in the kidney function which was evidenced by significantly lower urea and creatinine levels in rats after administration of Olmesartan in addition to glycerol. Therefore, Olmesartan has a reno-protective effect against glycerol-induced rhabdomyolysis via its antioxidant and anti-inflammatory properties, for the first time.

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