Impact of Blocking Renin Angiotensin Aldosterone Axis in Acute Kidney Injury

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ABSTRACT

Acute Kidney Injury (AKI) is a common health problem especially the drug induced AKI as a side or toxic effect during treatment of different medical disorders. Local Renin angiotensin aldosterone system (RAAS) has been described in addition to the systemic RAAS, and it is activated by renal injury. The aim of the current study was to evaluate and compare the renoprotective effect of inhibiting RAAS by losartan versus captopril on drug-induced AKI. 36 male albino rats constituted the animal model and have been divided into 6 groups (6 rats/group): control, AKI, AKI+losartan, AKI+captopril, losartan, captopril groups. Systolic blood pressure, glomerular filtration rate (GFR) have been measured. Serum samples were collected for measurement of urea, creatinine, cystatin-c, Monocyte Chemoattractant Protein-1 (MCP-1), Intercellular Adhesion Molecule 1 (ICAM-1) and Neutrophil gelatinase-associated lipocalin (NGAL). Kidney tissues were removed for measurement of tissue Malondialdehyde (MDA) and renal expression of Megalin, and kidney injury molecule 1 (KIM1). Both captopril and losartan attenuated drug induced AKI as revealed from the measured serum and tissue parameters. Captopril was superior to losartan on normalizing ICAM-1, megalin, and KIM-1, however; losartan improved GFR more than captopril. Other measured parameters showed no significant difference in AKI groups treated with losartan and groups treated with captopril.

Keywords: Acute Kidney Injury, losartan, captopril, RAAS

1. INTRODUCTION

Acute kidney injury (AKI), characterized by rapid loss of the ability of the kidneys to excrete wastes, concentrate urine, conserve electrolytes, and maintain fluid balance⁴. The kidneys are particularly susceptible to ischemic and toxic damage because they receive 20% of cardiac output. Certain medications are concentrated in the kidneys secondary to tubular secretion or reabsorption, which can predispose patients to renal injury. ARF can develop because of prerenal, intrinsic renal, or postrenal causes⁵. The Renin angiotensin aldosterone system (RAAS) was considered as an endocrine system with angiotensinogen, produced in the liver that is cleaved by renin released from renal juxtaglomerular cells. By this way, angiotensin I (AngI) is generated, which, in turn, is further cleaved by angiotensin-converting enzyme (ACE) activity of the lungs into the active form of Angiotensin II (AngII). AngII then binds to specific receptors in the adrenal cortex, resulting in the release of aldosterone. In this classical view, the cardinal function of the RAAS is maintaining of blood pressure by AngII-induced vasoconstriction and aldosterone-mediated sodium retention in the collecting duct⁶.
Local RAAS have been described to operate independently from their systemic counterpart. A local RAAS including all its components could have been shown in the proximal tubular cells of the kidney. Proximal tubular cells actively produce AngII and also secrete angiotensinogen into the urine. Intraluminal angiotensinogen may be converted in the distal tubules to AngII, and observations suggest that it leads to induction of sodium channels independent of aldosterone. Renal injury activates the local RAAS directly and indirectly\(^4\). The aim of the present study was to evaluate and compare the renoprotective effect of inhibiting RAAS by captopril versus losartan on acute kidney injury.

2. METHODS

**Study design and experimental groups**

36 male albino rats 4 months old, weighing 120-150 g.m constituted the animal model in this study. Rats were housed 3 per cage at a constant temperature (22-24 °C) and light controlled room on an alternating 12:12 h light-dark cycle and had free access to food and water. Rats were fed a standard commercial pellet diet. Animals handling, experimental design and experimental groups were approved by the local ethical and scientific committee.

**Experimental Groups**

Animals were divided into 6 groups (6 rats / group):

1. Group I control group → received saline by intraperitoneal (i.p) injection for 10 days.
2. Group II Gentamicin group (Acute renal failure group) → received gentamicin (garamicin, 80mg, Sandoz GMP, Switzerland) i.p injection as 100mg/kg/day for 10 days\(^5\).
3. Group III (losartan group) → received losartan per oral by oral gavage (losartan, 100mg, Hikma Pharmaceutical PLC, Jordan) as 10 mg/kg/day for10days\(^5\).
4. Group IV (ARF +losartan group) → received gentamicin injection 100mg/kg/day + oral losartan10 mg/kg/day for 10 days\(^5\).
5. Group V (captopril group) → received captopril per oral by oral gavage (Capoten, 25mg, pharmadex, American) as 10 mg/kg/day for 10 days\(^6\).
6. Group VI (ARF+captopril group) → received gentamicin injection 100mg/kg/day + oral captopril 10 mg/kg/day for 10 days\(^6\).

All experimental animals were weighed at the end of the study. The experimental rats were placed in metabolic cages for 24 h urine collection. The urine volume was also measured and then centrifuged to separate debris. The urine samples were kept at -80°C until further analysis.

**Glomerular filtration rate determination (GFR)**

GFR was calculated using the following formula after urine collection for 24 h and taking the body weight\(^7\).

\[
\text{GFR (ml/min/kg)} = \frac{\text{Urinary Creatinine (mg/dl) x Urine volume (ml) x1000 (g)}}{\text{Plasma creatinine (mg/dl) x Body weight (g) x 1440 (min)}}
\]

Systolic blood pressure was measured in the studied groups; then rats were anesthetized by ether inhalation, blood is withdrawn from retroorbital venous sinuses, for measurement of serum urea, creatinine, cystatin c , Monocyte Chemoattractant Protein-1 (MCP-1) , Intercellular Adhesion Molecule 1 (ICAM-1) and Neutrophil gelatinase-associated lipocalin (NGAL). Animals were sacrificed, kidneys removed for measurement of tissue Malondialdehyde (MDA) and renal expression of Megalin, and kidney injury molecule 1 (KIM1).

**Measurement of the arterial systolic blood pressure**

In the tail-cuff technique, animals were warmed for 30 min at 28°C in a thermostatically controlled heating cabinet (UgoBasille, Italy) for better detection of tail artery pulse, the tail was passed through a miniaturized cuff and a tail-cuff sensor that was connected to an amplifier (ML 125 NIBP, AD Instruments, Australia)\(^8\).

The tail cuff is a common and convenient noninvasive method to measure systolic pressure in rats. The tail cuff is inflated and then deflated. Pulsations disappear when the cuff is inflated. When the cuff is deflated, pulsations start appearing when the pressure in the cuff equals systolic pressure. The cuff is attached to a tail cuff sphygmomanometer, and BP is recorded on a chart\(^9\).

Systolic BP and heart rate of animals were indirectly measured each week with a noninvasive BP monitor (model ML 125 NIBP, ADInstruments Pty. Ltd., Sydney, Australia) from the tail of conscious rats by the tail-cuff technique for which all animals were pretrained until BP was steadily recorded with minimal stress and restraint. Training was conducted by the method described by Irvine et al.\(^8\). Systolic BP (cuff deflation pressure) was defined as the point at
which the cuff pressure corresponds to the restoration of the first caudal artery pulse. The average of at least three measurements was taken on each occasion. Heart rate was recorded automatically by a counter triggered by the pulse wave.

**Biochemical Measurements**

**Real-time RT-PCR**

Total RNA was isolated from kidney tissue, using the SV Total RNA Isolation Kit (Promega, Madison, WI) following the manufacturer’s instructions, including a DNase treatment step. 1 μg of RNA was then reverse transcribed into cDNA using the Superscript II Reverse Transcriptase Kit (Invitrogen) according to manufacturer’s protocol. Amplification and detection were performed in an optical 96-well plate with an ABI PRISM 7500 fast sequence detection system (Applied Biosystems, Carlsbad, California) using emission from SYBR Green (SYBR Green Master Mix, Applied Biosystems). After an initial activation step at 50°C for 2 min and a hot start at 95°C for 10 min., PCR cycles consisted of 40 cycles at 95°C for 15 s. and 60°C for 60 s. The sequences of PCR primer pairs used are shown in Table 1. Data were analyzed with the ABI Prism sequence detection system software and quantified using the v1.7 Sequence Detection Software from PE Biosystems (Foster City, CA). Relative expression of studied genes was calculated using the comparative threshold cycle method. All values were normalized to the GAPDH (glyceraldehyde-3-phosphate dehydrogenase) which was used as the control housekeeping gene.

**Table 1: Primer sequences used for RT-PCR**

<table>
<thead>
<tr>
<th>Primer</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIM-1</td>
<td>Forward primer 5'-AGAGAGAGCACGGACAGGCTT-3'</td>
</tr>
<tr>
<td></td>
<td>Reverse primer 5'-ACCCGTGGTAGTCCCCAACA-3'</td>
</tr>
<tr>
<td>Megalin</td>
<td>Forward primer 5'-GATGCTGTTGCTGCGATCG-3'</td>
</tr>
<tr>
<td></td>
<td>Reverse primer 5'-CATTGTACAGCAGGAAAAATCCCAC-3'</td>
</tr>
<tr>
<td>GAPDH</td>
<td>Forward: 5'-GATGC TGGTG CTGAG TATGT CG -3'</td>
</tr>
<tr>
<td></td>
<td>Reverse: 5'-GTGGTGCAAGATGACATTGCTCTGA -3'</td>
</tr>
</tbody>
</table>

**Determination of MDA**

Lipid peroxidations in kidney tissues were estimated colorimetrically by measuring thiobarbituric acid reactive substances (TBARS) by the method of Ohkawa et al. To 0.2ml of the sample, 8.1% Sodium dodecyl sulfate, 20% acetic acid and 0.8% TBA were added. Pyridine mixture was added, and the contents were vortexed thoroughly for 2 min. After centrifugation at 3000 rpm for 10 min, the upper layer was taken, and its OD was read at 532 nm. The levels of lipid peroxides were expressed as millimoles of thiobarbituric acid reactive substances (TBARS)/mg protein.

**Statistical analysis**

Data were coded and entered using the statistical package SPSS version 21 (IBM SPSS Statistics 21; IBM Corporation, New York, USA) for Microsoft Windows. Data was summarized using mean and standard deviation. Comparisons between groups were done using analysis of variance (ANOVA) with multiple comparisons post hoc Bonferroni test. P-values less than 0.05 were considered as statistically significant.

**3. RESULTS**

There was a significant (P≤0.05) increase of systolic blood pressure in AKI group compared to control group. Administration of either losartan or captopril in AKI groups caused significant (P≤0.05) decrease of systolic blood pressure compared to untreated AKI group. No significant difference observed in systolic blood pressure.
blood pressure in AKI groups treated with losartan or captopril (Figure 1).

Fig.1: Systolic blood pressure between study groups

GFR significantly (P≤0.05) decreased in AKI group compared to control group. Losartan or captopril therapy significantly (P≤0.05) increased GFR compared to untreated AKI group. Losartan showed significant (P≤0.05) increase of GFR compared to AKI group treated with captopril (figure 2).

There was a significant (P≤0.05) increase of serum urea, creatinine, cystatin, MCP-1, ICAM-1 and NGAL in AKI group compared to control group. Losartan or captopril therapy in AKI resulted in a significant (P≤0.05) decrease of serum urea, creatinine, cystatin, MCP-1, ICAM-1, and NGAL compared to AKI group. In most of the measured serum parameters, there was no significant difference in protective effect offered by losartan versus captopril except for ICAM-1 which showed significant (P≤0.05) decrease in AKI group treated with captopril compared to AKI group treated with losartan (table 2).

Table 2: Biochemical Parameters measured in serum of the studied groups

<table>
<thead>
<tr>
<th></th>
<th>Control (n=6 rats)</th>
<th>AKI (n=6 rats)</th>
<th>AKI + Losartan (n=6 rats)</th>
<th>AKI + Captopril (n=6 rats)</th>
<th>Captopril (n=6 rats)</th>
<th>Losartan (n=6 rats)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mg/dl)</td>
<td>35.50±8.96</td>
<td>80.18±6.85 *</td>
<td>49.31±7.87 #</td>
<td>53.33±9.04 *</td>
<td>41.25±5.18 #</td>
<td>37.65±3.67 #</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.13±0.05</td>
<td>1.53±0.56 *</td>
<td>0.67±0.20 #</td>
<td>0.50±0.23 #</td>
<td>0.14±0.06 #</td>
<td>0.14±0.06 #</td>
</tr>
<tr>
<td>Cystatin (mg/dl)</td>
<td>0.74±0.17</td>
<td>2.68±1.46 *</td>
<td>1.40±0.45 #</td>
<td>1.27±0.56 #</td>
<td>0.74±0.18 #</td>
<td>0.70±0.21 #</td>
</tr>
<tr>
<td>MCP-1 (Pg/ml)</td>
<td>37.15±2.38</td>
<td>105.8±22.09 *</td>
<td>57.21±15.98 #</td>
<td>40.60±14.23 #</td>
<td>31.34±4.73</td>
<td>34.2±6.786</td>
</tr>
<tr>
<td>ICAM-1 (Pg/ml)</td>
<td>137.4±6.63</td>
<td>180.1±15.58 *</td>
<td>55.84±8.39 #</td>
<td>38.87±6.56 #</td>
<td>33.07±4</td>
<td>35.35±5.06</td>
</tr>
<tr>
<td>NGAL (ng/dl)</td>
<td>142.88±3.6</td>
<td>214.3±11.62 *</td>
<td>133.34±31.82 #</td>
<td>117.05±20.73 #</td>
<td>102.16±6.78</td>
<td>108.71±7.9</td>
</tr>
</tbody>
</table>

AKI=Acute Kidney Injury, MCP-1= Monocyte Chemoattractant Protein-1, ICAM-1= Intercellular Adhesion Molecule 1, NGAL=Neutrophil gelatinase-associated lipocalin. *: statistically significant compared to corresponding value in control group. #: statistically significant compared to corresponding value in AKI group. $: statistically significant compared to corresponding value in AKI + losartan group at P≤0.05.

AKI group showed significant (P≤0.05) increase of renal expression of MDA and KIM-1 compared to control group. Losartan or captopril administered with AKI resulted in a significant (P≤0.05) decrease of MDA and KIM-1 expression compared to AKI group. There was no significant difference in MDA expression in AKI groups treated with losartan versus AKI group received captopril, however; KIM-1 expression showed significant (P≤0.05) reduction in AKI group treated with captopril compared to AKI group received losartan (table 3).
Megalin expression was significantly (P≤0.05) decreased in AKI group compared to control group. Administration of losartan or captopril to AKI groups resulted in a significant (P≤0.05) increase of Megalin expression compared to untreated AKI group. Captopril treatment in AKI caused a significant (P≤0.05) increase of megalin expression compared to AKI group treated with losartan (table 3).

<table>
<thead>
<tr>
<th></th>
<th>Control (n=6 rats)</th>
<th>AKI (n=6 rats)</th>
<th>AKI + Losartan (n=6 rats)</th>
<th>AKI + Captopril (n=6 rats)</th>
<th>Captopril (n=6 rats)</th>
<th>Losartan (n=6 rats)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA(mmol/mg)</td>
<td>2.1±3.29</td>
<td>8.7±3.65*</td>
<td>5.8±1.369**</td>
<td>2.68±1.16**</td>
<td>1.66±0.687</td>
<td>1.26±0.42747</td>
</tr>
<tr>
<td>KIM-1 (Relative Expression)</td>
<td>9.03±3.2</td>
<td>11.8±1.475*</td>
<td>4.08±2.146**</td>
<td>2.33±1.382**</td>
<td>1.21±0.25</td>
<td>1.21±0.329</td>
</tr>
<tr>
<td>Megalin (Relative Expression)</td>
<td>.25±.155</td>
<td>.150±.040*</td>
<td>.28±.12*</td>
<td>.97±12**</td>
<td>1.32±.4</td>
<td>1.5±.43</td>
</tr>
</tbody>
</table>

AKI=Acute Kidney Injury; MDA= Malondialdehyde; KIM-1= Kidney Injury Molecule- 1, *, statistically significant compared to the corresponding value in control group, #: statistically significant compared to the corresponding value in ARF group, $: statistically significant compared to the corresponding value in ARF + losartan group at P≤0.05.

4. DISCUSSION

Acute Kidney Injury is a common health problem especially the drug induced AKI as a side or toxic effect during treatment of different medical disorders. The existence of independent renin-angiotensin-aldosterone systems (RAAS) in several organs and tissues has been reported. All components of the renal RAAS are produced in the kidney, being completely independent of the systemic RAAS, and contribute to the progression of both acute and chronic kidney diseases(13). In the current study we evaluated the renoprotective effect of blocking RAAS at two different levels; by angiotensin converting enzyme inhibitor (ACEI) captopril and by AII receptor blocker (ARB) losartan.

The results of this study showed renoprotective effects of both captopril and losartan in AKI as revealed from their effects on systolic blood pressure, GFR, measured serum and tissue parameters. Captopril effect was superior to losartan regarding some of the measured biochemical parameters. However; losartan had a better effect on GFR. Supportive to our results Ots et al.(14), found that Captopril and losartan slow the rate of progression of the experimental renal disease. Increased AII activity has been recognized as a risk factor for progression of kidney disease. There is increasing clinical evidence that combining an ACE inhibitor with anARB reduces proteinuria and blood pressure in patients with renal disease(15). Abnormalities of renal perfusion possibly mediated by the renin-angiotensin system are responsible for the development of contrast-induced nephrotoxicity. Administration of the angiotensin-converting enzyme inhibitor, captopril, offers protection against the development of contrast-induced nephrotoxicity(16). In agreement with our results; Campbell et al.(17) reported that losartan has tissue-specific effects on endogenous levels of angiotensin. The absence of a reactive increase in endogenous kidney levels of Ang II indicates that this tissue is likely to be the most sensitive to AT1 receptor antagonism. Furthermore; Wen et al.(18), reported that Losartan decreased blood cystatin C levels and attenuated renal fibrosis, tubular necrosis, and inflammatory cell infiltration. A one-year course of antihypertensive therapy with either losartan or captopril significantly reduces Urinary albumin: creatinine (UAC) ratio in hypertensive type 2 diabetic patients with early nephropathy. The reduction in UAC with each treatment is similarly related to decrements in ABP(19). Losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy, and it was generally well tolerated(20).

Cystatin C is a 122 amino acid low molecular weight protein that is a member of the cysteine proteinase inhibitors [21]. It is produced at a constant rate by all nucleated cells and is freely filtered by the glomerulus, reabsorbed and catabolized, but not secreted by the renal tubules(21). Unlike creatinine, serum cystatin C concentration appears to be independent of age, sex, and muscle mass(22). Cystatin C appeared to be the most sensitive indicators of nephrotoxicity, with significant changes occurring as early as day 1 and importantly before alterations in serum creatinine or BUN(23).

Inhibition of the RAS by either an ARB or ACEI leads to a reversible reduction in intraglomerular pressure in most nephrons. In the case of preexisting renal insufficiency, however, fewer functional nephrons, "remnant nephrons," are present and thus function at a relatively higher baseline pressure to maintain stable renal function\textsuperscript{[24].}

MCP-1 is a chemokine family and a potent chemotactic factor for monocytes\textsuperscript{[25].} Increased expression of MCP-1 was described in experimental and human forms of glomerulonephritis\textsuperscript{[26].} The MCP-1 is a biomarker for mononuclear inflammatory processes that occur following ischemia-induced acute kidney injury and acts as a mediator of acute ischemic and toxic kidney injury\textsuperscript{[27].}

MCP-1 expression is increased in glomeruli and tubulointerstitial space in hypertensive nephrosclerosis associated with Ang II-dependent hypertension\textsuperscript{[28].} Several lines of evidence suggest that Ang II may directly contribute to the induction of MCP-1 in hypertensive nephrosclerosis: Ang II has been shown to increase MCP-1 synthesis in vascular smooth muscle cells in vitro\textsuperscript{[29]} and in vivo\textsuperscript{[30].} Blockade of Ang II in experimental models of immune-mediated glomerulonephritis reduced the induction of MCP-1\textsuperscript{[31].} Also, mechanical forces such as glomerular hypertension could directly contribute to MCP-1 expression, which is increased by shear stress in cultured endothelial cells in vitro\textsuperscript{[32].}

In vitro treatment of rat vascular smooth muscle cells with Ang II upregulates MCP-1, and blockade of AT1R with losartan prevents MCP-1 expression and monocytes migration into the vessel wall and other target organs\textsuperscript{[29].}

Adhesion molecules are required for leukocyte adhesion during inflammation. Leukocyte adhesion to endothelial cells leads to inflammation and extension of cellular injury. ICAM-1 plays an important role in the pathophysiology of AKI\textsuperscript{[33].}

Deficiency of ICAM-1 may have conferred protection against LPS-induced ARF not only by decreasing neutrophil adhesion but also by abrogating signaling events that occur in endothelium upon ligation of ICAM-1\textsuperscript{[34].}

In agreement with our results; blocking RAAS with valsartan in combination with fluvastatin (a statin) in atherosclerosis mouse model, reduced the level of atherosclerotic lesions, superoxide anion, and the expression level of MCP-1 and ICAM-1, indicating that blocking inflammation and oxidative stress has beneficial effects on endothelium\textsuperscript{[35].} Indeed, clinical studies showed a reduction in cardiovascular events beyond blood pressure lowering such as positively altering endothelium/vascular wall structure which in turn mediates reduction of cardiovascular disease. Several RAAS inhibitors such as ACEI and ARB improve endothelial activity and vascular function by increasing NO bioavailability\textsuperscript{[36].}

In hypertensive patients, ARB irbesartan has been shown to improve endothelial function and vascular reactivity and to reduce the levels of CRP, ICAM-1, IL-6, and oxidative stress marker 8-isoprostane\textsuperscript{[37].} In vitro and in vivo studies have shown that ARB olmesartan inhibits Ang II-induced aortic vascular smooth muscle cells migration and therefore prevents vascular remodeling\textsuperscript{[38].}

Neutrophil gelatinase-associated lipocalin (NGAL), a small 25-kDa protein of the lipocalin family, was discovered through a genome-wide analysis of kidney genes that are induced in response to experimental acute kidney injury in animals. NGAL is a biomarker of tubular damage since it was a secreted tubular protein that entered both urine and serum rapidly after the onset of AKI\textsuperscript{[39].}

Cai and colleagues\textsuperscript{[40]} reported that several different molecular forms of NGAL were found in human urine and that the monometric form is predominantly secreted by cultured renal tubular epithelial cells, whereas the dimeric form is predominantly secreted by neutrophils\textsuperscript{[40].} Inflammation induced by various stresses increases serum NGAL, while impaired renal absorption increases urinary NGAL excretion\textsuperscript{[41].}

In agreement with our study; Zhang et al.\textsuperscript{[42]} showed decreased serum NGAL levels in animal models of renal interstitial fibrosis treated with ACEI. However; Stine et al.\textsuperscript{[43]} showed no significant change in urinary NGAL in patients with diabetic nephropathy treated with ARBs.

MDA is a marker of lipid peroxidation. In accordance with our findings; Ramsammy and colleagues\textsuperscript{[44]} have examined the role of lipid peroxidation in gentamicin-induced acute renal failure. Moreover; Wang et al.\textsuperscript{[45]} studied the effect of blocking RAAS by direct renin inhibitor, aliskiren on acute kidney injury induced by ischemia-reperfusion and showed increased lipid peroxidation and decrease of renal MDA after aliskiren administration.

Megalin is a 600-kDa single transmembrane receptor protein. It belongs to the low-density lipoprotein receptor family. Megalin is responsible for the normal tubular reabsorption of virtually all filtered proteins, mediating the recovery of essential substances that otherwise would be lost in the urine\textsuperscript{[46]}. 

In the kidney, megalin is expressed in the proximal tubule and at a much lower level in glomerular podocytes(47). Changes in megalin mRNA expression have been demonstrated in different models of AKI. In LPS-induced acute endotoxemia and AKI, a decrease in renal megalin mRNA expression was observed. This decrease was associated with increased urinary albumin excretion(48).

Renin is a ligand for megalin. Partial megalin deficiency led to substantial urinary renin excretion which underlines the role of megalin in its tubular retrieval(49). A role for megalin in the transcytosis of RAS components has thus been demonstrated(50). The early proximal tubule displays very effective, megalin-dependent endocytotic uptake and intracellular storage of renin and AGT from the ultrafiltrate(51).

KIM-1 is a Type I transmembrane glycoprotein which is localized in the apical membrane of dilated tubules in acute and chronic injury(52). Kim-1 is believed to play a role in regeneration processes after epithelial injury and in the removal of dead cells in the tubular lumen through phagocytosis(53). A reduction in proteinuria with renin-angiotensin-aldosterone blockade is accompanied by a reduction in urinary KIM-1 excretion(54).

In the kidney, Kim-1 is upregulated in a wide variety of human diseases and in various animal models. A large amount of KIM-1 protein is also shed into the urine, making it a useful urinary biomarker for kidney injury(53). Kim-1 also functions as a scavenger receptor, mediating the uptake of modified low-density lipoprotein and necrotic cell debris(52).

5. CONCLUSION

Both captopril and losartan attenuated drug-induced acute renal injury as revealed from the measured serum and tissue parameters. Captopril was superior to losartan on normalizing ICAM-1, megalin, and KIM-1, however; losartan improved GFR more than captopril. Other measured parameters showed no significant difference in AKI groups treated with losartan and groups treated with captopril.

We recommend further studies by other blockers of RAAS and histopathological evaluation of renal tissue for more examination of the state of the cortex and medulla of the kidney.

ACKNOWLEDGMENT:
We would like to thank the technicians at Physiology and Pharmacology Departments, Faculty of Medicine, Cairo University.

CONFLICT OF INTEREST:
There is no conflict of interest.

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