# Histological Assessment of Pioglitazone Preventive Effect in Glycerol Contrast-Induced Nephropathy in Rats

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**Abstract:** Contrast-induced nephropathy (CIN) remains as a problem of radiographic procedures with high incidence and mortality rates. This study aims to histologically assess the ability of Iohexol to induce nephropathy in rats injected with Glycerol; then investigate the Pioglitazone renoprotective effect on this CIN model in rats. 35 male Albino Wistar rats were randomly divided into 5 groups (n=7/group): healthy (A), Glycerol (B), Glycerol+ Iohexol (C), Glycerol + Iohexol + Pioglitazone (D), Pioglitazone alone (E). Groups (B), (C), and (D) were intramuscularly injected with Glycerol 25% (10 ml/kg). Iohexol (350 mg I/ml, 8,6 ml/kg) was injected through a caudal vein in groups (C) and (D). Pioglitazone (10 mg/kg) was orally administered for 4 days, to groups (D) and (E). Rats were sacrificed on the fifth day. Kidney samples were collected for histological assessment. The results show that the histopathological scores and kidney weight / body weight ratio in group (C), were significantly increased compared with group (B) and (A). These changes were significantly reversed in rats treated with Pioglitazone (group D).

In conclusion, Iohexol could cause renal injury in rat kidneys previously damaged by Glycerol. Pioglitazone was able to protect the kidneys from histological alterations.

**Keywords:** Kidney, Contrast-Induced Nephropathy (CIN); Contrast medium, Iohexol; Pioglitazone..

## INTRODUCTION

Contrast media (CM) are frequently used for various diagnostic and interventional procedures including X-rays, computed tomography, and coronary artery interventions [1]. Contrast-induced nephropathy (CIN) is a serious complication associated with the use of iodinated radiocontrast agents. It considers a leading cause of acute kidney injury and is associated with significant prolonged hospital stay, higher in-hospital clinical complications and increased medical costs. Furthermore, 1-year mortality rates are also increased [2]. CIN is the third most common cause of hospital-acquired acute kidney injury (AKI), accounting for between 11% and 50% in patients with multiple risk factors, notably diabetes, preexisting renal insufficiency and old age [3].

CIN is defined as an increase in serum creatinine of 0.5 mg/dL (44 mmol/L), or a 25% relative increase in serum creatinine levels assessed within 48 hours after a radiological procedure [1]. Iohexol is a low osmolar non-ionic radiocontrast agent (low osmolar contrast medium LOCM), with improved safety and tolerability compared to classic high osmolar agents [1]. Nevertheless, CIN incidence remains high after its intravascular administration in high-risk patients, most notably in those with estimated glomerular filtration rate eGFR < 30 ml/Kg/1.73 $m^2$ [4]. On the other hand, many studies didn't find any significant difference in the incidence rate between different types of contrast media [5,6].

The exact underlying mechanisms of this impairment have not yet been fully elucidated but are likely to involve the interplay of several effects on renal tubules including renal hypoperfusion and medullary ischemia. The direct tubular cell toxicity exerted by the contrast medium molecules play also an important role [7-9]. Reactive oxygen species have also been implicated as a contributing factor [9,10]. The inflammatory process is particularly significant in the pathophysiology as well [8].

Many experimental and clinical studies are being conducted with the aim of preventing CIN. There is no available adopted prophylactic or therapeutic agent for CIN, and treatment options are limited to supportive care, e.g. hydration with normal saline solution [11,12].

Pioglitazone is a member of Thiazolidinediones, which are a new class of antidiabetic drugs that improve insulin sensitivity and lipid metabolism, acting like agonists of peroxisome proliferator-activated receptor-γ (PPAR-γ), a member of nuclear receptor superfamily [13]. Reports have demonstrated that pioglitazone show several beneficial renoprotective effects [13,14], but its role in preventing CIN is unclear.

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## RESEARCH OBJECTIVES

The aim of this study is to investigate the histological kidney alterations following Iohexol administration. The second aim is to determine whether pioglitazone has a renoprotective effect in this CIN model, using histological analysis.

## MATERRIALS AND METHODS

### Chemicals

- Pioglitazone hydrochloride was obtained from Abhilasha Pharma PVT.LTD. A suspension (1mg/ml) in carboxymethylcellulose CMC 0.5% w/v was prepared.
- Glycerol was obtained from Surechem Products LTD, diluted in normal saline solution 0.9% to reach a 25% v/v concentration.
- Iohexol (omnipaque) (350 mg I/ml) was obtained from GE healthcare company.

### Animals

In this study, 35 male Albino Wistar rats (230–300 g) were used. Rats were housed in standard plastic cages on sawdust bedding in an air-conditioned room at 22 ± 1◦C, with a 12-hour light/dark cycle. They were allowed free access to a standard rat diet and water. Animals were left one week for adaptation before starting our experiment. Animals were randomly divided into five groups:

- Group A: control.
- Group B: Glycerol only (Gly).
- Group C: Glycerol+ contrast medium Iohexol (Gly+ CM).
- Group D: Glycerol+ Iohexol+ Pioglitazone (GLY+CM+PIO).
- Group E: Pioglitazone (PIO).

### The Experimental Protocol

The protocol followed in this study was first suggested by Duan *et al.* [15]. 24 hours after water deprivation, an initial Kidney injury was induced in rats by intramuscular injection of Glycerol 25% at a single dose of 10 mL/kg [15,16] in groups (B), (C) and (D), half dose into each hind limb. Drinking water and food were then resumed ad libitum. 30 minutes later, Pioglitazone (10 mg/kg) [17,18], was administered orally to the animals in groups (D) and (E) using an intubation needle. Treatment was continued daily for 4 days. 24 hours after Glycerol injection, Iohexol (350 mg I/ml) at a single dose of 8.6 mL/kg [15,16] ,was injected through a caudal vein over a period of 2 minutes to the animals in groups (C) and (D). All animals were sacrificed on the fifth day under deep ethyl ether anesthesia. Kidneys were excised immediately for histopathological studies.

### Kidney Weight / Body Weight Ratio

Rat kidneys weight / body weight ratio were calculated, then converted to percent.

### Histopathological Assessment

Kidneys obtained from all animals were dicapsulated, and sectioned longitudinally into two equally sized pieces then fixed in 15% buffered formalin solution for 24 hours. The specimens were dehydrated in a graded ethanol, cleared in xylene, and then embedded in paraffin wax. 4-5 micrometre-thick serial sections were cut using a microtome (Leica). Heamatoxylin and eosin staining were used for histopathlogical examination using a light microscope with camera connected to a computer for photographic documentation. A Minimum of 10 fields for each kidney slide were assessed.

The results were scored semiquantitatively and in descriptive form. The examinations focused on renal tubules for the presence of dilatation and vacuolation. Special attention was paid to the features indicating tissue apoptosis and necrosis. Interstitial edema and medullary congestion were also assessed. The severity of these lesions was determined using scores on a scale of grade (0): negative, grade 1: minimal, grade 2: mild, grade 3: moderate, and grade 4: severe [19]. This study examined also the renal glomerular injury, hemorrhage, inflammation, fibrinoid and hyaline dystrophies, where the presence of these injuries was grade 1, and their absence was grade 0.

### Statistics

Statistical analysis was performed using prism (Version 5) statistical package. Numerical data were expressed as (mean ± standard error of the mean SEM). Data were evaluated by one-way analysis of variance (ANOVA), followed by Tukey's test multiple comparison. Histological Analysis which used categorical ordinal data were evaluated by the non-parametrical Mann– Whitney U test. The frequency of categorical binary data was evaluated using ficher's

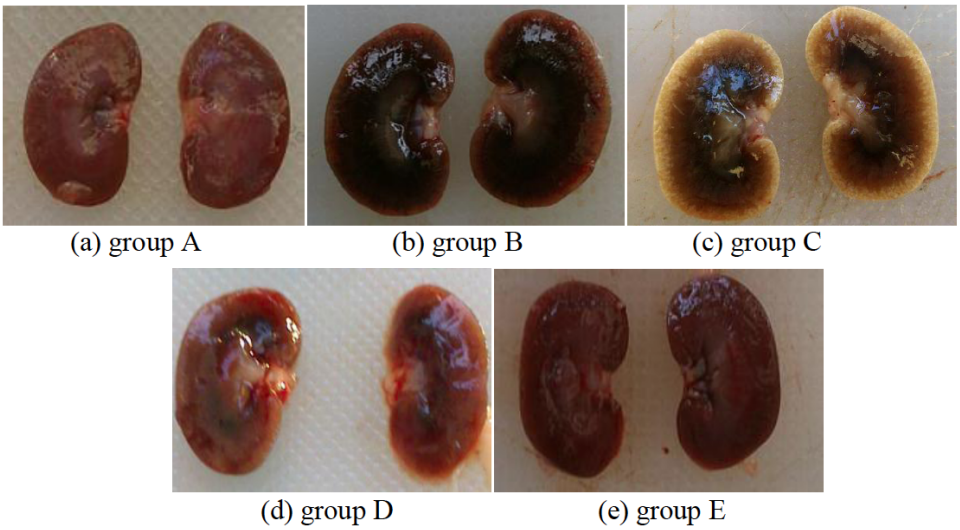


**Figure 1:** The macroscopic evaluation of kidney sections in different groups in CIN model in rats.

exact test. Five-percent-error risk P values <0.05 were considered as statistically significant.

## RESULTS

### Macroscopic Evaluation

In control groups A and E, kidneys have normal macroscopically appearance. They were bean- shaped, surrounded by an easy-to-remove capsule. Their surface was smooth and red-brown in color. The sections showed the cortex and medulla, which were different in shade. The blue-red medulla was indented towards the yellowish-red cortex dividing it into renal columns (Figure **1a**, **1e**). Kidneys in injured groups B and C were bigger than those in control group, with different macroscopic morphology. They showed pale pink with multiple microabscesses in the cortex and dark brown medulla with noticed congestion and edema. The border between the medulla and cortex was clear (Figure **1b**, **1c**). These morphological changes were more clear in group C (Figure **1c**), but were markedly reversed in the preventive group D (Figure **1d**), where kidneys looked, to a certain extent, similar to those of control groups.

### The Percentage of Kidney Weight / Body Weight Ratio (%)

Administration of glycerol alone (group B) significantly increase the percentage of kidney weight / body weight ratio compared with group (A) (P<0.001). Iohexol injection significantly aggravated this increase (P<0.001). This percentage was significantly decreased in group (D) (P<0.001). No statistically significant difference was found between groups A and E (P>0.05). The results are shown in Table **1** and Figure **2**.

**Table 1: Pioglitazone Effects on Kidney Weight / Body Weight Ratio in CIN Model Expressed as (Mean ± SEM)**

| Groups | Kidney weight/ body weight ratio (%) |
|---|---|
| Group A: Control | 0.312 ± 0.008 |
| Group B: GLY | 0.383 ± 0.014 |
| Group C: GLY + CM | 0,525 ± 0,013 |
| Group D: GLY + CM+ PIO | 0,359 ± 0.011 |
| Group F: PIO | 0.301 ± 0.01 |

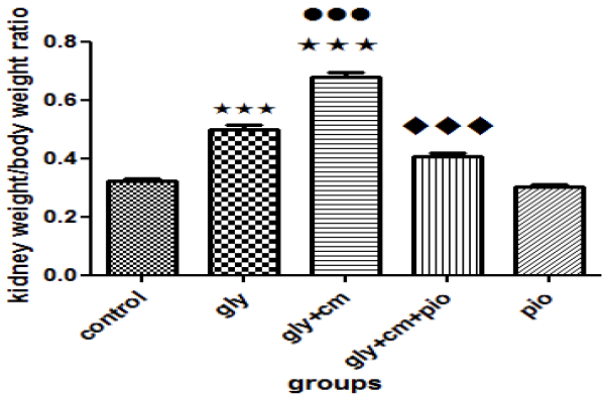


**Figure 2:** Pioglitazone effects on the percentage of kidney weight / body weight ratio in CIN model expressed as (mean ± SEM).

*** P<0.001 compared with control group. ●●● P<0.001 compared with GLY group. ♦♦♦ P<0.001, compared with GLY+CM group. GLY: glycerol, CM: contrast medium, PIO: pioglitazone.

**Table 2: Effects of Pioglitazone on Histopathological Scores of Renal Tubules, Interstitial Edema and Medullary Congestion, Expressed as as the Frequency of Injured Animals in each Group**

| Features Groups | (0) | (1) | (2) | (3) | (4) | Significance | (0) | (1) | (2) | (3) | (4) | Significance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group A | 0 | 7 | 0 | 0 | 0 | | 2 | 5 | 0 | 0 | 0 | |
| Group B | 0 | 0 | 1 | 4 | 2 | *** | 0 | 0 | 0 | 6 | 1 | ** |
| Group C | 0 | 0 | 0 | 3 | 4 | *** | 0 | 0 | 0 | 2 | 5 | **● |
| Group D | 0 | 0 | 2 | 5 | 0 | # | 0 | 0 | 2 | 5 | 3 | ## |
| Group E | 0 | 7 | 0 | 0 | 0 | | 5 | 2 | 0 | 0 | 0 | |
| **Features Groups** | **Tubular Apoptosis** | | | | | | **Interstitial edema** | | | | | |
| | **(0)** | **(1)** | **(2)** | **(3)** | **(4)** | **Significance** | **(0)** | **(1)** | **(2)** | **(3)** | **(4)** | **Significance** |
| Group A | 5 | 2 | 0 | 0 | 0 | | 6 | 1 | 0 | 0 | 0 | |
| Group B | 0 | 0 | 0 | 5 | 2 | ** | 0 | 0 | 5 | 2 | 0 | ** |
| Group C | 0 | 0 | 0 | 0 | 7 | ●● *** | 0 | 0 | 2 | 3 | 2 | ** |
| Group D | 0 | 0 | 2 | 5 | 0 | ### | 0 | 0 | 1 | 5 | 1 | |
| Group E | 5 | 2 | 0 | 0 | 0 | | 3 | 4 | 0 | 0 | 0 | |

| Features Groups | Medullary congestion | | | | | |
|---|---|---|---|---|---|---|
| | (0) | (1) | (2) | (3) | (4) | Significance |
| Group A | 3 | 4 | 0 | 0 | 0 | |
| Group B | 0 | 2 | 5 | 0 | 0 | ** |
| Group C | 0 | 0 | 2 | 2 | 3 | ** ●● |
| Group D | 0 | 1 | 1 | 2 | 3 | |
| Group E | 5 | 2 | 0 | 0 | 0 | |

** P<0.01 compared with control group. *** P<0.001 compared with control group.● P<0.05 compared with GLY group. ●● P<0.01 compared with GLY group. # P<0.05 compared with GLY+CM group. ## P<0.01compared with GLY+CM group. ### P<0.001compared with GLY+CM group.
GLY: glycerol, CM: contrast medium, PIO: pioglitazone.

**Table 3: Effects of Pioglitazone on Glomerular Injury, Fibrinoid Dystrophy and Hyaline Dystrophy, Expressed as Frequency of Injured Animals in each Group**

| Groups feature | Glomerular injury | | | Fibrinoid dystrophy | | | Hyaline dystrophy | | |
|---|---|---|---|---|---|---|---|---|---|
| | injury | No injury | Significance | injury | No injury | Significance | injury | No injury | Significance |
| Group A | 0 | 7 | | 0 | 7 | | 0 | 7 | |
| Group B | 7 | 0 | *** | 2 | 5 | | 5 | 2 | |
| Group C | 7 | 0 | *** | 7 | 0 | *** ● | 7 | 0 | *** ● |
| Group D | 1 | 6 | ## | 0 | 7 | ### | 0 | 7 | ### |
| Group E | 2 | 5 | | 0 | 7 | | 0 | 7 | |

*** P<0.001 compared with control group. ● P<0.05 compared with GLY group. # P<0.05 compared with GLY+CM group. ### P<0.001 compared with GLY+CM group. GLY: glycerol, CM: contrast medium, PIO: pioglitazone.

## Microscopic Evaluation

Histopathological changes in all groups kidneys were examined and scored, and the results are provided in Tables **2**,**3** and **4**. In control groups A and E, the microscopic pictures of the kidneys were normal. The renal tubules were regularly arranged and characterized by clearly-visible empty lumen without pathological deposits and shaded with a brush border. They were lined with one-layer cubic epithelium with poorly-marked margins. The glomerular and bowman capsules appearances were normal (Figure **3**, **a1** and **e1**). Some specimens showed mild changes in the

**Table 4: Effects of Pioglitazone on Acute Inflammation and Frequency of Injured Animals in each Group**

| Groups features | Acute inflammation | | | Hemorrhage | | |
|---|---|---|---|---|---|---|
| | injury | No injury | Significance | injury | No injury | Significance |
| Group A | 0 | 7 | | 0 | 7 | |
| Group B | 2 | 5 | | 1 | 6 | |
| Group C | 7 | 0 | *** ● | 7 | 0 | *** ●● |
| Group D | 0 | 7 | ### | 3 | 4 | |
| Group E | 1 | 6 | | 2 | 5 | |

*** P<0.001 compared with control group. ● P<0.05 compared with GLY group. ●● P<0.01 compared with GLY group. ### P<0.001 compared with GLY+ CM group. GLY: glycerol, CM: contrast medium, PIO: pioglitazone.

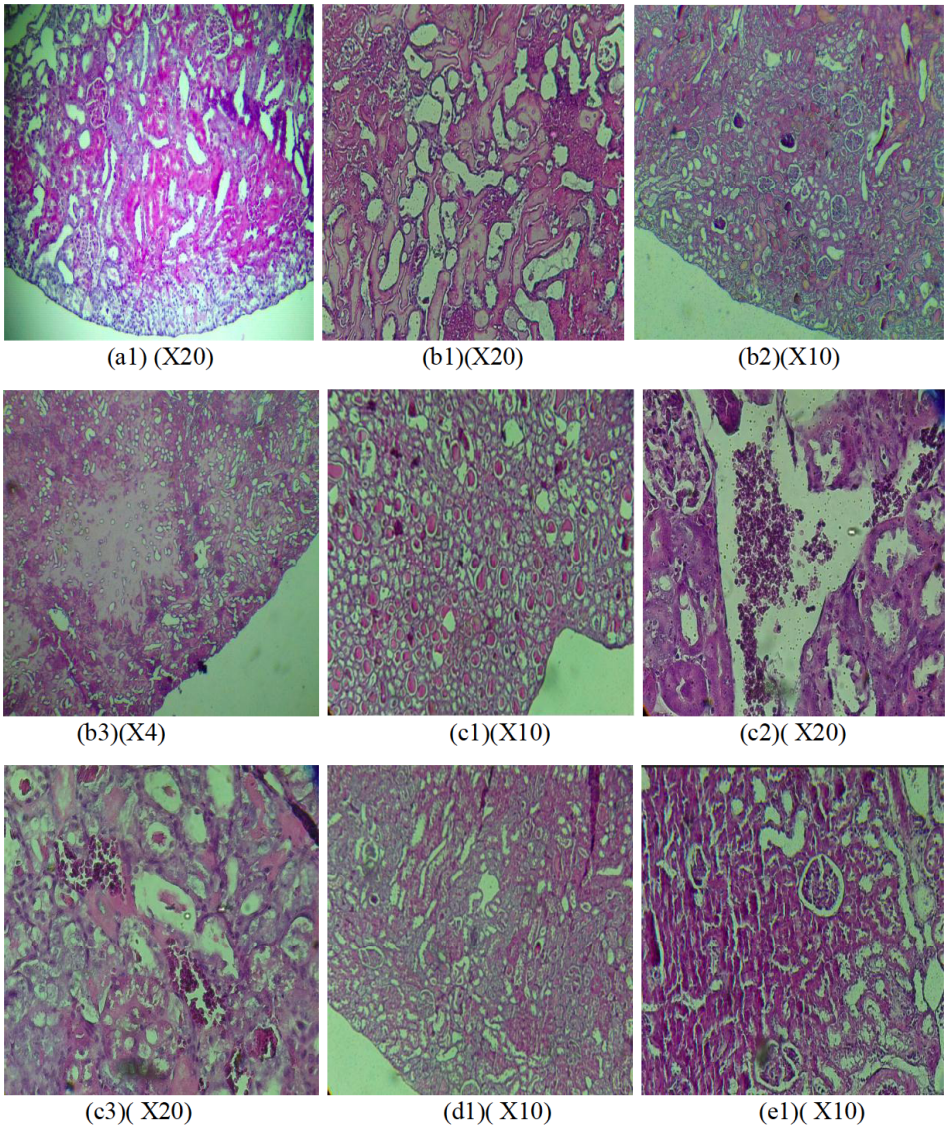


**Figure 3:** histopathological assessement of pioglitazone effects on CIN model in rats. renal sections were stained with hematoxylin and eosin and examined with light microscope.

(**a1**) represent Kidney section of a control rat showing normal architecture, normal glomerulus, normal tubules and their lined cells. (**b1**), (**b2**) and (**b3**) represent Kidney section of a glycerol treated rats showing glomerular deformation, tubular dilatation, vacuolation, swelling and degeneration of their lined epithelial cells, vascular congestion, fibrinoid distrophy and hyaline dystrophy. (**c1**), (**c2**) and (**c3**) represent Kidney section of Iohexol treated rats, showing vascular congestion (**c1**), glomerular injury and inflammatory cells infiltration, swelling and degeneration of tubular lined epithelial cells in (**c2**) and hyaline dystrophy in (**c3**). (**d1**,**d2**) represent kidney section of group D rats treated with pioglitazone, showing the enhancement in tubular and glomrular injuries and other pathologic alterations. (**e1**) represents kidney sections in control group treated with pioglitazone alone.

renal tubular histology and mild edema and congestion. By contrast, severe lesions were seen in group B kidneys tubules injected by glycerol, which show dilatation, vacuolation and typical apoptotic morphology including swelling, fragmentation and deformation of tubular lined epithelial cells and formation of apoptotic bodies (Figure **3**, **b1**). Renal tubular scores were significantly higher compared with control group A (P<0.01, P<0.001) (Table **2**). There is also minimal to mild medullary congestion and mild to moderate interstitial edema (Figure **3**, **b2**). These injuries were significantly different from control group (P<0.01). The sings of glomerular injury were observed in this group represented as mesangial extracellular matrix deformation, focal necrosis and glomerular capillary congestion (P<0.001 compared with control group). Fibrinoid and hyaline dystrophies were also observed (Figure **3**, **b1**, **b3**) unlike the control group. Mono-nuclear and polymorphonuclear leukocytes infiltration were seen in the tubules and interstitium at high magnification. Hemorrhage was also observed in some samples. All these histological lesions were aggravated in group C rats injected with glycerol, and the contrast medium Iohexol. The microscopic examination show moderate to severe tubular dilatation and apoptosis (P<0.001 compared with control group) and vacuolation (P<0.01 compared with control group). The markedly widened lumen of some tubules was filled with degenerated and desquamated epithelial cells.

The very severe necrosis represented as flattened, damaged, or completely destroyed cells. This was more pronounced in the cortical segments of the proximal tubules. (Figure **3**, **c2**). A statistically-significant increase in medullary congestion scores (Figure **3**, **c1**), and in the number of apoptotic cells was observed in this group C compared with group B (P<0.01). The examinations show moderate to severe interstitial edema (P<0.01 compared with control group). The hemorrhage was significantly aggravated compared with control group A (P<0.001), and with group B (P<0.01). Glomerular injury was also observed in this group (P<0.001 compared with control group) (Figure **3**, **c2**). On the other hand, the scores of fibrinoid and hyaline dystrophy and inflammation were significantly increased compared with control group (P<0.001) and with group B (P<0.05) (Figure **3**, **c3**). In rats treated with pioglitazone (group D), the tubular lesions were significantly reduced compared with group C (tubular dilatation P<0.05, tubular vacuolation P<0.01, and tubular apoptosis (P<0.001)) (Figure **3**, **d1**). There was a significant amelioration in glomerular lesions (P<0.01) and acute inflammation compared with group C (P<0.001) (Figure **3**, **d1**). The fibrinoid and hyaline dystrophies and acute inflammation was almost alleviated in group D (P<0.001 compared with group C).

## DISCUSSION

Contrast-induced nephropathy is still a significant source of hospital morbidity and mortality with the increasing use of iodinated contrast media in diagnostic imaging and interventional procedures [7]. Particularly in patients with preexisting renal insufficiency [2,9].

Glycerol was injected intramuscularly to provoke an initial injury that simulates patients' risk factors, and makes kidneys more sensitive to the contrast mediumtoxicity; then the low osmolar contrast medium Iohexol was injected intravenously.

This simple and easy protocol, which does not require surgical procedures [20] or pre-use of certain drugs [21,22] that might affect the results, have been implemented by several previous studies [15,16,23]. Since healthy animals have high resistance to CIN [20], this protocol induces an optimal CIN model.

The nephropathy occurrence was detected histopathologically using light microscope to detect the type and the extent of injuries in different kidney parts.

Glycerol injection causes significant morphological changes in rat kidneys, concerning shape, shade and weight. Injuries were also observed microscopically in renal tubules, specially into renal proximal tubules, manifested as tubular dilatation, vacuolation and apoptosis. Glomerular injury, medullary congestion and interstitial edema were also observed. All these injuries were significantly aggravated when administering Iohexol. Besides the signs of inflammation, hemorrhage, hyaline and fibrinoid dystrophy in this group animals compared with normal rats, or whose subjected to glycerol alone. Development of edema and enlargement of kidney after Iohexol administration which was evident by significant increase in kidney weight-to-body weight ratio, also confirm the significant renal toxicity. Thus, this study results indicated that Iohexol administration could aggravate nephropathy in rats with preexisting renal injury induced by Glycerol. These histologic alterations, notably the tubular damage signs, have been reported earlier in several previous studies [16,23]. The results get along as well with Boyacioglu M. *et al* study [24] and Tervahartiala *et al*. study [25], which indicated that administration of Iohexol alone can induce an obvious renal injury. Vacuolar transformation, interstitial edema, and tubular

degeneration following the contrast medium administration have also been reported earlier in some studies [15,26], despite the absence of the significant difference in serum biomarkers of renal function in these studies.

Numerous pathways have been suggested to explain these histological injuries. Administration of the contrast medium causes intrarenal vasoconstriction as a result of several mechanical and hemodynamical disturbances. The subsequent reduction in blood flow lead to hypoxia and renal ischemic injury that is most pronounced in the external region of renal medulla, an area uniquely susceptible to ischaemic injury [2,8-10].

During ischemia, greater amounts of reactive oxygen species ROS are generated as a result of perturbations in the mitochondrial electron transport chain and excessive ATP hydrolysis. Hydrogen peroxide $H_2O_2$ can scavenge NO, a well known vasodilator, through the formation of peroxynitrite. This will lead to worsening renal vasoconstriction and increases the production of angiotensin-II leading to greater vasoconstrictor effects and worsening the case [8,10].

These excessive amounts of ROS mediate also the damage of cell membranes leading to cellular apoptosis and necrosis, particularly represented in S3 segments of proximal renal tubules of the outer medulla [10]. This damage may be aggravated by direct toxic effects of the contrast medium molecules. This effect referred mainly to the activation of intrinsic cellular apoptotic pathway [8], and to the toxic effect of free iodine, released from the contrast medium, to the cellular membranes [27]. On the other hand, direct DNA damage and some cell organelles injuries (mitochondria or endoplasmic reticulum) due to hypoxia, during CIN process, play also an important role [28,29].

Affected cells rupture and the cellular components spill into the surrounding tissue space, evoking an inflammatory response due to the increased production of pro-inflammatory cytokines, such as TNF-α, IL-B [28].

All these factors lead to renal tubular dysfunction and alter the mechanisms regulating tubular cells transport. Acute tubular necrosis (ATN) is the main result [1].

Fibrinoid and hyaline dystrophy can be reffered to the cellular and vascular injuries and the subsequent increase in endothelial permeability, interstitial protein infiltration and hyalin-like protein drops filling the entire cytoplasm.

Although the preventive effects of many drugs against CIN have been investigated, there is no standardized treatment for this disorder [11,12]. Thus in an attempt to find a new preventive option, this study aimed to histopathologically determine the possible role of a peroxisome proliferator activated gamma receptor agonist, pioglitazone, in the prevention. It can beneficially act on most major players involved in CIN progression [13], and thus exceed other known preventive options' effects.

As presupposed, the results proved that the renal histology started to improve following the administration of pioglitazone (10 mg/kg for 4 days).

This protection effect on renal tissues has also been earlier in other models of renal impairment induced by cyclosporine [17], acute nephrotic syndrome [18], and polycystic kidney disease [30].

Pioglitazone has many benefic effects that may explain its prevention. Functional PPAR-ɣ receptors have been identified in renal glomerular and tubular segments and are abundant in inner medulla. The effects of Pioglitazone might or might not be directly mediated by PPAR-γ activation [31]. Pioglitazone, can improve renal nitric oxide (NO) bioavailability, which has a vasodilative effect on renal arterioles and improve renal endothelial functions [13,14,31]. Thiazolidindiones reduce the secretion of the potent vasoconstrictor endothein-1 [13,31]. Several studies found that Pioglitazone counteract renin-angiotensin system effect in renal vasculature [13,32]. These properties can improve renal blood flow and alleviate ischemic injury resulting from contrast medium administration. Pioglitazone has also antifibrotic [13, 33], anti- inflammatory and anti-apoptotic effects [31]. On the other hand several systemic actions, such as reductions in blood glucose and blood pressure levels, can be involved in this compound renoprotective properties [13]. As well as its antioxidant properties [32,34,35,36], which due to improve the transcription of some antioxidant enzymes at the kidney level. This study proved also that Pioglitazone does not have any effect in normal conditions, unless a previous lesion is there.

## CONCLUSION

The contrast medium Iohexol can exacerbate the renal injury initially induced by glycerol and cause

several marked histopathological alterations, most notably in proximal tubular segments. Pioglitazone, can provide a promising approach in this type of renal injury prevention. Moreover, it has the advantage to show its effects in a short time of administration, and therefore enhance the compliance.

However, its total renoprotective effects and the exact mechanisms involved in this protection, and doses that can be used should be further explored by future clinical trials, especially on high risk diabetic nephropathy patients already treated with this drug.

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