Original article

Introduction
Diabetes mellitus (DM) is currently a major health problem all over the world. It is a chronic metabolic disorder resulting from an interaction of hereditary and environmental factors [1]. It is classified into type 1 (insulin-dependent) and type 2 (non-insulin-dependent) DM. Type 2 DM is a heterogeneous disorder characterized by insulin resistance [2]. The incidence of type 2 DM is increasing significantly and is associated with high morbidity and mortality rates [3]. Increased glucose states are associated with many renal complications [4]. The recent studies have demonstrated a higher incidence of nephropathy in type 2 DM than in type 1 DM patients [5]. Diabetic patients are at a higher risk for ischemic problems caused by decreased blood flow [6]. With increasing duration and severity of ischemia, cell damage can develop predisposing to a spectrum of reperfusion-associated pathologies, collectively called reperfusion injury [7]. Imbalance between reactive oxygen species (ROS) and antioxidant capacity as well as nitric oxide (NO) plays an important role in mediating cell damage during ischemia–reperfusion (I/R) injury [8–11]. Inflammation also contributes substantially to the pathogenesis of I/R, with a central role for adhesion molecules and cytokines [12].

Various drug therapies are used in the treatment of type 2 DM and its complications [13]. Of the currently available oral antidiabetic agents, sulfonylureas are widely used by many diabetic patients. However, sulfonylureas potently and persistently stimulate insulin secretion irrespective of blood glucose levels, thereby causing hypoglycemia, which is a common undesirable side effect [14]. As such, there is a need to develop efficient new therapeutic strategies for the treatment of type 2 DM. During the investigation of new antidiabetic drugs that do not have the disadvantages of sulfonylureas, glucagon-like peptide 1 (GLP-1) attracted attention. The insulinotropic action of GLP-1 is glucose dependent; therefore, the risk for hypoglycemia is minimized [15].

Keywords:
diabetes mellitus, exenatide, glucagon-like peptide 1, ischemia–reperfusion, kidney, oxidative stress

Aim
Diabetes mellitus (DM), especially type 2, is a major health problem, and diabetic nephropathy is the main cause of end-stage renal disease. Renal ischemia–reperfusion (I/R) injury is common in diabetic patients. Recent studies reported increased vulnerability of kidneys to I/R injury in diabetic rats. In view of the reported efficacy of glucagon-like peptide-1 (GLP-1) on I/R injury, this study was designed to assess the effect of exenatide (GLP-1) on renal I/R in type 2 DM.

Materials and methods
Type 2 DM in rats was induced by administration of nicotinamide (110 mg/kg, intraperitoneal), 15 min before a single dose of streptozotocin (45 mg/kg, intraperitoneal). Renal I/R was performed in both diabetic and normal rats. The protocol comprised ischemia for 30 min followed by reperfusion for 24 h aymd a treatment period with exenatide 2 weeks before induction of ischemia.

Results
Renal I/R in diabetic rats induced marked renal dysfunction associated with a significant increase in malondialdehyde, nitric oxide, and tumor necrosis factor α levels. Antioxidant enzymes such as reduced glutathione and superoxide dismutase were significantly reduced. Exenatide treatment significantly normalized these biochemical parameters compared with diabetic I/R rats.

Conclusion
In conclusion, exenatide protects renal I/R injury in type 2 DM. These findings have major implication in the treatment of ischemic injury that is prone to develop in DM.

Keywords:
diabetes mellitus, exenatide, glucagon-like peptide 1, ischemia–reperfusion, kidney, oxidative stress
Recent evidence has demonstrated the beneficial effects of GLP-1-associated drugs in the treatment of type 2 DM [16]. GLP-1 is a 30-amino acid hormone secreted by the small intestine in response to nutrient ingestion and degraded by the enzyme dipeptidyl peptidase-IV. GLP-1 acts through the GLP-1 receptor, which is a G-coupled protein receptor expressed not only in the gastrointestinal tract but also in the nervous system, heart, vascular smooth muscles, proximal tubules, and glomeruli of the kidney [17,18]. GLP-1 increases insulin secretion from pancreatic β-cells and reduces glucagon release from α-cells through induction of adenylyl cyclase and cyclic adenosine monophosphate production [19,20].

GLP-1 receptor agonists extend the effects of endogenous GLP-1 by resisting enzymatic degradation [21]. The GLP-1 receptor agonist exendin-4 is a 39-amino acid peptide that was originally isolated from the salivary secretions of the Gila monster lizard [22]. A synthetic version of exendin-4, exenatide, is currently used for the treatment of type 2 DM [21]. The administration of GLP-1 receptor agonists results in greater improvements in glycemic control when administered as monotherapy or in combination with one or two oral antidiabetic drugs in patients with type 2 DM. Moreover, these drugs seem to exert a number of other pleiotropic effects on diabetic nephropathy [23,24]. GLP-1 have reported efficacy in I/R injury [25,26]. Thus, this study was designed to assess the effect of exenatide (GLP-1 receptor agonist) on renal I/R in type 2 DM.

Materials and methods

Animals
This study was conducted on 40 adult Wistar albino male rats, 6–8 weeks old, weighing between 170 and 200 g. The animals were housed in the Animal Laboratory at the Medical Research Center of Benha Faculty of Medicine. They were housed at room temperature (25°C) and 12/12 h light/dark cycle. All rats were fed a standard diet and water.

Groups of the experiment
The animals were randomly divided into five groups of eight rats each.

Group I (the control group) included normal sham-operated rats (underwent all surgical procedures without I/R in normal rats).

Group II (the diabetic group) included diabetic sham-operated rats (underwent all surgical procedures without I/R in diabetic rats).

Group III (the I/R group) included IR-induced normal rats. On day 28, ischemia was produced for 30 min, followed by reperfusion for 24 h.

Group IV (the DM+I/R group) included IR-induced diabetic rats. After induction of diabetes, on day 28, I/R was induced.

Group V (the exenatide+DM+I/R group) included exenatide-treated rats. In diabetic rats, on day 14, exenatide was injected at a dose of 10 mcg, subcutaneously, twice a day for 2 weeks [27]. On day 28, I/R was induced.

Chemicals used

Streptozotocin
It was purchased from Sigma-Aldrich Chemical Co., St. Louis, Mo, USA. It was dissolved in freshly prepared sodium citrate buffer pH 4.5.

Nicotinamide
It was purchased from Sigma-Aldrich Chemical Co. It was dissolved in normal physiological saline.

Exenatide
It was purchased from Sigma-Aldrich Chemical Co. It was supplied as a sterile solution for subcutaneous injection (250 μg/ml).

Induction of diabetes mellitus
Type 2 DM was induced in rats by administering nicotinamide (110 mg/kg, intraperitoneal) 15 min before a single dose of streptozotocin (45 mg/kg, intraperitoneal) [28]. The animals were allowed to drink 5% glucose solution overnight to overcome drug-induced hypoglycemia. Control rats were injected with the buffer alone. Diabetes was verified 72 h later by measuring blood glucose levels (after an overnight fasting) with the use of glucose oxidase reagent strips. Rats having blood glucose level of 250 mg/dl or greater were considered to be diabetic. Four weeks elapsed between the induction of diabetes and ischemic injury.

Renal ischemia–reperfusion injury
Diabetic and normal rats were anesthetized with ketamine (60 mg/kg, intraperitoneal) and diazepam (5 mg/kg, intraperitoneal). After anesthesia, the animal was fixed in supine position on the operating table and the abdominal skin was shaved and disinfected with povidone–iodine solution. All rats underwent surgical exposure of the left and right renal pedicles through midline incision. To induce renal ischemia, both renal
pedicles were occluded for 30 min using a nontraumatic vascular clamp. After 30 min of occlusion, the clamps were removed and the kidneys were subjected to reperfusion. The abdomen was properly irrigated with isotonic saline, and then the abdominal incision was closed by means of continuous stitches using vicryl 2/0 sutures.

Urine sample collection
Urine samples were collected for 24 h (at the end of the reperfusion periods) after placing each rat in a metabolic cage, and, to avoid urea degradation, urine samples were maintained frozen. Urinary albumin was measured by means of quantitative reaction using a Sigma Diagnostic Kit (Sigma-Aldrich Chemical Co., St. Louis, Mo, USA).

Blood sample collection
Blood samples were taken 24 h after ischemia (reperfusion period). A craniocaudal incision of about 2 cm was made, parallel and slightly to the left of the sternum through the skin and pectoral muscles to expose the ribs. A blunt curved forceps was then inserted between the fifth and sixth ribs, through the intercostals muscles. The gap was widened so that the rapidly beating heart becomes visible, and then the blood samples were taken from the right ventricle.

Biochemical assessment
Blood samples were allowed to clot at room temperature and sera were separated by means of centrifugation at 3000 rpm for 15 min. Sera were used for biochemical assessment of serum glucose using the glucose oxidase–peroxidase method (GOD–POD Kit, Accurex Biomedicals Pvt. Ltd., Mumbai, India), blood urea nitrogen (BUN) (Jaffe's method), creatinine (the DAM method), and aspartate aminotransferase (AST), using standard diagnostic Kits (Sigma-Aldrich Chemical Co., Sigma Diagnostic Kit (Sigma-Aldrich Chemical Co., St. Louis, Mo, USA)).

Kidney biopsies
The previous incision was continued through the animal's anterior abdominal wall. The abdominal cavity was entered by cutting the muscles and peritoneum. The kidneys were exposed and then freed from the surrounding tissue. Kidneys were quickly excised and portions of kidney tissues were homogenized in a saline solution (0.9%), centrifuged at 3000 rpm for 15 min, and the supernatant was kept at −20°C and used for the determination of antioxidant parameters such as malondialdehyde (MDA) [29], superoxide dismutase (SOD) [30], and reduced glutathione (GSH) [31]; however, NO was estimated using the method described by Lepoivre et al. [32].

Results

Effect of exenatide on serum glucose concentration
Administration of nicotinamide (110 mg/kg, intraperitoneal) followed by STZ (45 mg/kg, intraperitoneal) resulted in a significant elevation of serum glucose level in the DM group compared with the control group (P < 0.05), but no significant difference was found on comparing the I/R group and the control group. On performing renal I/R to diabetic rats, they produced a significant increase in serum glucose concentration as compared with both diabetic animals (P < 0.05) and I/R animals (P < 0.05). Moreover, pretreatment of rats with exenatide (10 μg/kg) produced a significant hypoglycemic effect (P < 0.05) as compared with the DM+I/R group (Table 1).

Effect of exenatide on renal function
There was a significant increase in BUN and serum creatinine in both the DM group (P < 0.05) and the I/R group (P < 0.05) compared with the normal control group. In addition, serum level of AST was found to be significantly increased in the I/R group compared with the normal control group (P < 0.05), whereas this increase did not reach statistical significance on comparing the DM group and the control group.

Table 1 Effect of exenatide on serum glucose concentration and renal function after renal ischemia–reperfusion in normal and diabetic rats

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal control group</th>
<th>DM group</th>
<th>I/R group</th>
<th>DM+I/R group</th>
<th>Exenatide-treated (exenatide+DM+I/R) group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum glucose (mg/dl)</td>
<td>97.3 ± 9.2</td>
<td>375 ± 8.9*</td>
<td>102.4 ± 3.2</td>
<td>489 ± 12.1*</td>
<td>101 ± 11.9*</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>23.9 ± 1.4</td>
<td>30.2 ± 1.7*</td>
<td>34.6 ± 2.4*</td>
<td>50.1 ± 6.1*</td>
<td>26 ± 1.9*</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.34 ± 0.05</td>
<td>0.62 ± 0.04*</td>
<td>1.27 ± 0.31*</td>
<td>2.67 ± 0.13*</td>
<td>0.38 ± 0.22*</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>86.7 ± 11.5</td>
<td>90.5 ± 8.1</td>
<td>514 ± 25.6*</td>
<td>753 ± 22.1*</td>
<td>253 ± 62.1*</td>
</tr>
<tr>
<td>Urine albumin (mg/24 h)</td>
<td>1.07 ± 0.06</td>
<td>2.9 ± 0.14*</td>
<td>3.4 ± 0.16*</td>
<td>5.03 ± 0.2*</td>
<td>1.9 ± 0.12*</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; I/R, ischemia–reperfusion; *Significant difference (P < 0.05) compared with the control group; †Significant difference (P < 0.05) compared with the DM group; ‡Significant difference (P < 0.05) compared with the I/R group; §Significant difference (P < 0.05) compared with the DM+I/R group.
Diabetic animals that underwent renal I/R exhibited a significant increase in the serum concentrations of BUN, creatinine, and AST as compared with DM animals \((P < 0.05)\), suggesting a significant degree of glomerular dysfunction. Serum concentrations of BUN, creatinine, and AST were also significantly increased in the DM+I/R group compared with the I/R group \((P < 0.05)\). Pretreatment of rats with exenatide produced a significant reduction in the serum levels of these parameters as compared with the DM+I/R group \((P < 0.05)\). As regards urine albumin, the results showed a significant increase in 24-h urine albumin in both the DM group \((P < 0.05)\) and the I/R group \((P < 0.05)\) compared with the normal control group. Performing renal I/R to diabetic rats was associated with a significant increase in urine albumin as compared with the DM group \((P < 0.05)\) and the I/R group \((P < 0.05)\). Exenatide supplementation resulted in a significant reduction in 24-h urine albumin \((P < 0.05)\), compared with the DM+I/R group (Table 1).

### Effect of exenatide on lipid peroxidation and antioxidant enzymes

MDA content of the renal tissue was found to be significantly increased in both the DM group \((P < 0.05)\) and the I/R group \((P < 0.05)\) compared with the normal control group. Moreover, the renal MDA content in diabetic rats was elevated after induction of I/R injury, compared with the DM group \((P < 0.05)\) and the I/R group \((P < 0.05)\). However, the exenatide-treated group significantly decreased the I/R-induced elevation in renal MDA level as compared with the DM+I/R group \((P < 0.05)\) (Table 2).

As regards the antioxidant enzyme activity, the renal tissue SOD and GSH contents were significantly decreased in both the DM group \((P < 0.05)\) and the I/R group \((P < 0.05)\) compared with the normal control group. Moreover, I/R in diabetic rats demonstrated a significant decrease in renal tissue SOD and GSH contents in comparison with DM animals \((P < 0.05)\) and I/R animals \((P < 0.05)\), whereas in the exenatide-treated group, renal SOD and GSH contents were found to be significantly increased \((P < 0.05)\), compared with the DM+I/R group.

The serum TNF-α level was significantly increased in the DM group \((P < 0.05)\) and the I/R group \((P < 0.05)\) compared with the normal control group. In DM+I/R rats, serum TNF-α level was significantly higher compared with the DM group \((P < 0.05)\) and the I/R group \((P < 0.05)\). The exenatide-treated group had significantly lower serum TNF-α level \((P < 0.05)\) compared with the DM+I/R group.

The levels of NO were increased in the DM group \((P < 0.05)\) and the I/R group \((P < 0.05)\) as compared with the normal control group. In addition, NO levels showed a significant increase in diabetic animals that underwent renal I/R, compared with either the DM group \((P < 0.05)\) or the I/R group \((P < 0.05)\). The exenatide-treated group demonstrated a significant decrease in NO level \((P < 0.05)\) as compared with the DM+I/R group.

### Discussion

DM, especially type 2, causes organ dysfunction and increases the sensitivity of organs to damages. DM and hyperglycemia render the kidney more susceptible to ischemic injury \([33]\). Ischemia of the kidney starts a series of incidents including cellular dysfunction and necrosis \([34]\). However, reperfusion can paradoxically create more tissue injury. It seems that the effects of I/R injury on renal cells are multifactorial, involving hypoxia, free radical damage, and inflammatory responses \([35]\). There is growing evidence that treatment with GLP-1 receptor agonists may be effective in decelerating the progression of I/R injury \([25,26]\). Therefore, in the present study, we examined the effect of renal ischemia for 30 min on renal functions, proinflammatory cytokines TNF-α, and oxidant markers in STZ-nicotinamide-induced diabetic rats and the possible role of exenatide in these changes.

### Table 2 Effect of exenatide on lipid peroxidation and antioxidant enzymes after renal ischemia-reperfusion in normal and diabetic rats

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal control group</th>
<th>DM group</th>
<th>I/R group</th>
<th>DM+I/R group</th>
<th>Exenatide-treated (exenatide+DM+I/R) group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malondialdehyde (nmol/g)</td>
<td>2.1 ± 0.27</td>
<td>4.8 ± 0.26*</td>
<td>6.2 ± 0.16*</td>
<td>11.7 ± 0.43*</td>
<td>3.2 ± 0.31*</td>
</tr>
<tr>
<td>Superoxide dismutase (U/g)</td>
<td>7.08 ± 0.51</td>
<td>5.43 ± 0.32*</td>
<td>4.84 ± 0.80*</td>
<td>2.71 ± 0.88*</td>
<td>6.7 ± 0.63*</td>
</tr>
<tr>
<td>Reduced glutathione (μmol/g)</td>
<td>38.4 ± 2.5</td>
<td>27.6 ± 1.8*</td>
<td>25.1 ± 1.3*</td>
<td>21.3 ± 2.1*</td>
<td>32.9 ± 2.3*</td>
</tr>
<tr>
<td>Serum tumor necrosis factor α (ng/ml)</td>
<td>6.73 ± 0.35</td>
<td>16.35 ± 0.64*</td>
<td>18.66 ± 0.72*</td>
<td>31.15 ± 0.83*</td>
<td>0.9 ± 0.48*</td>
</tr>
<tr>
<td>Nitric oxide (μmol/g)</td>
<td>0.5 ± 0.02</td>
<td>0.7 ± 0.03*</td>
<td>0.8 ± 0.03*</td>
<td>1.5 ± 0.8*</td>
<td>0.6 ± 0.08*</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; I/R, ischemia–reperfusion; *Significant difference \((P < 0.05)\) compared with the control group; †Significant difference \((P < 0.05)\) compared with the DM group; ‡Significant difference \((P < 0.05)\) compared with the I/R group; §Significant difference \((P < 0.05)\) compared with the DM + I/R group.
In the present study, diabetic rats showed a significant increase in serum blood glucose, BUN, serum creatinine, urine albumin, TNF-α, NO, and MDA, as well as a significant decrease in antioxidant enzymes (SOD and GSH). Induction of I/R in diabetic rats caused significant increase in serum blood glucose, BUN, serum creatinine, urine albumin, TNF-α, NO, MDA and AST as well as significant decrease in SOD and GSH, as compared with diabetic rats. At the same time, there was a negative correlation between exenatide and these parameters. These findings suggest the possible role of proinflammatory cytokines, TNF-α, and oxidative markers in the pathogenesis of ischemic injury in diabetic kidney.

The present study showed a significant increase in the blood glucose in diabetic rats, with a further increase by induced renal I/R injury. These results are in agreement with those reported by Mohamed et al. [33].

As regards kidney functions, diabetic rats showed impaired renal function in the form of significant increase in BUN and serum creatinine levels associated with increased 24-h urinary albumin excretion as compared with normoglycemic ones. These findings, which are in agreement with several studies [33,36], are considered as an indicator of deteriorated renal function [37,38]. In addition, the data of the current work confirmed the findings of Yousef et al. [39] and Gabr et al. [40], who found that the combination of renal ischemia with diabetes raised the renal dysfunction more than did diabetes alone, leading to a marked increase in serum urea, creatinine, AST, and urine albumin, suggesting a significant impairment of the glomerular function. These results emphasize the hypothesis of Melin et al. [41], who stated that the combination of both diabetes and renal ischemia plays a major role in the development of diabetic nephropathy. Type 2 diabetes can cause increased sensitivity to renal I/R as observed experimentally through several mechanisms. One possible mechanism was hyperglycemia and its secondary effects such as formation of advanced glycosylated end products and increased oxidative stress. Hemodynamic alterations could be a contributing factor. Formation of NO could also be involved. Moreover, shortage of insulin could play a role in the increased sensitivity to I/R [33].

In addition, both diabetic rats and rats exposed to renal I/R exhibited an increase in oxidative stress product including tissue MDA. There was a depletion of the antioxidant enzyme pool, demonstrated by the declined activity of SOD and GSH in kidney tissues. This notion was confirmed by Vaghasiya et al. [42], who emphasized that the oxidative stress is implicated both in the complications of type 2 diabetes and renal I/R and that the combined oxidative stress from these two sources may, thus, increase the total level of ROS. Kakadiya et al. [43] documented that during renal I/R much of the tubular and glomerular dysfunction occurs during the reperfusion period following anoxia. Generation of ROS has been postulated as one of the major factors, contributing to this reperfusion injury [43]. In renal I/R injury, ROS react with lipids, leading to lipid peroxidation of biological membranes [44], which in turn impacts enzymatic processes, such as ion pump activity, that inhibit transcription and repair of DNA [9,45].

The present study showed a significant rise in serum TNF-α level in diabetic rats and in ischemic rats when compared with normal control rats. However, the marked rise was found in diabetic ischemic rats. These findings are in agreement with several investigations that demonstrated a significant rise in the serum level of TNF-α in renal I/R injury as well as in diabetic rats [38,40,46]. The enhanced TNF-α production in ischemic diabetic rats may result from the hyperglycemia [47] and the increased generation of ROS [48]. Hyperglycemia-induced oxidative stress and products of lipid peroxidation likewise serve as activators of transcription factors, leading to induction of gene expression of proinflammatory cytokines and release of many inflammatory cytokines, such as TNF-α and IL-6 [49]. TNF-α may produce a renal injury, inducing apoptosis, necrotic cell death, alterations of intraglomerular blood flow, and glomerular filtration rate as a result of the hemodynamic imbalance between the vasoconstrictive and vasodilatory mediators [40]. Impairment of the barrier function of the glomerular capillary wall leads to the enhanced albumin permeability [50]. At the molecular level, TNF-α augments the release of many inflammatory factors from renal mesangial cells [51]. These findings are in agreement with those of Araki et al. [52] and Kher et al. [53], who reported that the oxidative stress and the inflammatory response might play a pathophysiological role in renal I/R injury in type 2 diabetes. This may confirm the results of the present study in which there was a significant positive correlation between serum TNF-α and renal tissue content of MDA.

Another point of interest in the present study was to investigate the involvement of NO in the development of renal I/R injury in DM. NO was significantly elevated in renal tissue in diabetic ischemic rats. This result is in agreement with the findings of many authors who documented that inducible nitric oxide synthase is activated in the kidney of rats, soon after the induction
of diabetes [54,55]. The NO system may be involved in the increased sensitivity to I/R in DM. The reaction of NO with $O_2$ results in peroxynitrite formation, a potent and aggressive cellular oxidant, and causes the formation of 3-nitro-1-tyrosine. Nitrite/nitrate levels, as the end products of NO conversion, were increased in blood plasma and aortic tissue in diabetic animals compared with nondiabetic ones [55], which was confirmed by elevated NO level in the current study.

Exenatide treatment in diabetic I/R rats reduced the oxidative stress and the biomarkers of the inflammation, which are determinant factors in the course of renal disease. Treatment with exenatide prevented renal I/R-induced lipid peroxidation and protected the kidneys from severe attenuation of antioxidant enzyme activity in rats exposed to the renal I/R. In addition, it improved the functional renal parameters such as BUN and creatinine, AST, and urine albumin.

Several mechanisms might be responsible for the renoprotective effects of exenatide against renal I/R. First, the restoration of normoglycemia, because glucose metabolism is stimulated over fatty acid metabolism [56]. An increased sensitivity to ischemia has been demonstrated when blood glucose level was raised by dextrose infusion or intraperitoneal glucose injection in combination with renal I/R in dogs [57]. In our study, we found that glucose controlled by means of exenatide pretreatment could have a protective effect against renal I/R in type 2 DM.

In conclusion, exenatide might reduce apoptosis and oxidative stress. Timmers et al. [58] demonstrated that the activity of the antioxidant enzymes was higher in animals treated with exenatide and nuclear oxidative stress was reduced. In the current study, decreased MDA activity and increased SOD and GSH in the treatment with exenatide demonstrated the reduction in nuclear oxidative stress. The results of the present study are in agreement with those performed by others, which have been suggesting an antioxidant and anti-inflammatory effect of incretin modulators, due to attenuation of the deleterious effects of oxidative stress and protection against the cytokine-induced apoptosis and necrosis [59,60]. Therefore, the protection afforded by exenatide reflects improved glucose metabolism as well as anti-inflammatory, antioxidant, and antiapoptotic effects.

In conclusion, type 2 diabetes provoked an exaggerated renal I/R injury in STZ–nicotinamide-treated rats. Exenatide treatment attenuated renal I/R in diabetic rats by modifying the oxidative stress and the inflammation processes.

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Nil.

### Conflicts of interest
There are no conflicts of interest.

### References


31 Moron MS, Depierre JW, Mannervik B. Levels of glutathione, glutathione reductase and glutathione S-transferase activities in rat lung and liver. Biochim Biophys Acta 1979; 582:67–78.