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Renoprotective Effect of Sitagliptin (Dipeptidyl Peptidase- 4 Inhibitor) aganist Cisplatin Induced Nephrotoxicity in Mice

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Back Ground and Objectives: Despite the therapeutic benefits of cisplatin(CDDP) , its use clinically is often limited due to dose-related nephrotoxicity. Meanwhile, DPP 4 inhibitors could attenuate kidney injury, so the present work aimed to investigate the effect of one of DPP 4 inhibitors (sitagliptin) on cisplatin induced nephrotoxicity in mice .
Materials and Methods: 48 male balb-c mice were equally divided into 4 groups, control, sitagliptin group, cisplatin group and cisplatin plus sitagliptin group. The mice were sacrificed at 72 h after cisplatin injection. Blood urea nitrogen (BUN) & serum creatinine, renal tissue of antioxidant enzymes, lipid peroxidation, TNF-alpha (TNF-α) were measured as well as histopathological scoring of renal injury.
Results: The results demonstrated that sitagliptin significantly ameliorated the nephrotoxic effect of cisplatin with increased activity of antioxidant enzymes, improved kidney function, renal histopathological scoring and decreased tissue level of TNF-α. **Conclusions:** It can be concluded that sitagliptin may play a protective effect against cisplatin induced acute nephrotoxicity via antioxidant and anti-inflammatory pathway.

Keywords: Sitaglipin; Cisplatin; Nephrotoxicity; TNF-alpha; Antioxidants.

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1. INTRODUCTION

Cisplatin (CDDP), a noncycle-dependent cytotoxic platinum derivative, has been frequently used in different solid tumors, including gastric, testicular, urologic, head, neck, and ovarian cancer [1]. Despite the therapeutic benefits, its use in clinical practice is often limited owing to dose-related toxicity.

Clinical application shows that CDDP-induced acute nephrotoxicity can even force an interruption of the treatment of cancers. CDDP has multiple intracellular effects, including regulating genes, causing direct cytotoxicity with reactive oxygen species production, and induction of apoptosis. The nephrotoxic potential of CDDP has been attributed to the overgeneration of reactive oxygen species (ROS) induced by the accumulation of CDDP in the renal tubular cells. Additionally, the reduction of the antioxidant enzymes activities also causes morphological damage to the intracellular organelles [2]. Different researches have showed a significant insight into the mechanisms leading to inflammation in CDDP-induced acute kidney injury [3]. There is a growing evidence, indicating that CDDP induces remarkable activation of NF-kB in kidneys, and the inhibition of NF-kB activation is capable of attenuating CDDP-induced renal injury [4,5].

Tumor necrosis factor- α (TNF- α), as a consequence, is increased in cisplatin injury [6-8] and coordinates the activation of a large network of chemokines and cytokines in the kidney following cisplatin injection [8]. Moreover, inhibition of either TNF- α production or its activity ameliorates cisplatin-induced renal dysfunction and structural damage [9].

Glucagon-like peptide-1 (GLP-1) is a gut incretin hormone,whose mimetics have been used as a therapeutic agent for type 2 diabetes. It stimulates pancreatic beta cell proliferation and insulin secretion in a glucose-dependent manner [10]. However, this peptide is almost immediately degraded by dipeptidyl peptidase (DPP) 4 in the circulation. DPP 4 has a wide variety of substrates that have important roles in cell migration and differentiation, glucose regulation, metabolism, and inflammation [11]. Sitagliptin, a highly selective DPP 4 inhibitor, is currently used in the treatment of type 2 diabetic patients to improve glucose tolerance by increasing the half-life of GLP-1 and glucose-dependent insulinotropic peptide (GIP) [12]. Some studies have shown that DPP 4 inhibitors attenuate kidney injury in diabetic animal models [13-15]. DPP 4 inhibition also protects the kidney against ischemia-reperfusion injury (IRI) [16]. Tissue protective effects of GLP-1 activation or DPP 4 inhibition have also been demonstrated in different organs, including IRI of the lung during transplantation [17-19] and the outcome of myocardial infarction [20,21].

The purpose of the present study was to determine the protective effect of sitagliptin (DPP 4 inhibitors) on cisplatin-induced renal injury and to examine its mechanism.

2. MATERIALS AND METHODS

2.1 Drugs and Chemicals

Cisplatin was purchased from Sigma Chemical Co., St Louis, MO, USA, Sitagliptin phosphate monohydrate powder was purchased from Santa Cruz Biotechnology, Santa Cruz, CA, USA & TNF-α kit from Linco Research, Inc., St Charles, MO, USA. Other chemicals and reagents were purchased from Sigma (Sigma Chemical Co., St Louis, MO, USA).

2.2 Animals and Drug Treatment

Male balb-C mice were given a standard laboratory diet and water ad libitum, and were cared for under a protocol approved by the Institutional Animal Care and Use Committee of our University. At the start of the experiments, the mice were 8–10 weeks of age, weighing 25–30 g. To obtain an optimal dose of cisplatin and time of treatment, dose-dependent (10, 15 or 20 mg/kg) and time-dependent (24, 48, 72 or 96 h) experiments were performed. Renal injury examined by renal function and histological findings was clearly seen with a dose of 20 mg/kg cisplatin at 72 h after cisplatin treatment. Therefore, 20 mg/kg cisplatin and 72 h treatment were applied throughout the study. In the case of sitagliptin treatment, a dose dependant experiment (40, 80 or 160 mg/kg sitagliptin) was performed. Significant protective effects of sitagliptin on the cisplatin-induced renal injury were obtained at a dose of 160 mg/. This concentration of sitagliptin was used throughout the experiment. The mice were divided into four groups: control (received saline orally and ip injection of control buffer) (n/12), sitagliptin (160 mg/kg; dissolved in saline) (n/12), cisplatin (20 mg/kg; dissolved in control buffer) (n/12) and cisplatin plus sitagliptin (n/12).

Control buffer and cisplatin were injected intraperitoneally. Sitagliptin was administrated by oral gavage once a day until the mice were sacrificed at 72 h after cisplatin injection.

2.3 Renal Function Monitoring

On the day of the sacrifice, blood was collected immediately. Urea nitrogen and creatinine levels in blood were measured using an enzymatic method (SRL, Tokyo, Japan).

2.4 Histological Examination

The mice kidneys were sectioned in blocks and fixed in 4% paraformaldehyde, then dehydrated in graded concentrations of alcohols and embedded in paraffin. The kidney block was cut into 5 mm sections and stained with periodic acid–Schiff (PAS) reagents. Tubular damage in PAS-stained sections was graded using the percentage of cortical tubules showing epithelial necrosis: 0= normal; 1<10%; 2=10–25%; 3=26–75%; 4>75%. Tubular necrosis was defined as the loss of the proximal tubular brush border, blebbing of apical membranes, tubular epithelial cell detachment from the basement membrane or intraluminal aggregation of cells and proteins. The morphometric examination was performed in a blinded manner by two independent investigators.

2.5 Biochemical Measurements

Biochemical measurements were performed on kidney tissues of the mice. A portion of isolated kidney tissue from each mouse was homogenized in 10% (w/v) Tris-HCl buffer (pH 7.0) and are used for the measurement of SOD, CAT, GPx, GSH and total lipid peroxidation (LPO).

2.6 Measurement of Superoxide Dismutase (SOD) Activity

SOD activity in kidney tissues was determined based on the ability of the enzyme to inhibit nitroblue tetrazolium (NBT) reduction by superoxide [22]. In brief, into an incubation medium containing 0.1 ml of test sample, 2.55 ml of phosphate buffer, 0.2 ml EDTA/NaCl, 0.1 ml

NBT, and 0.05 ml riboflavin (to a total volume of 3 ml) were added. The tubes then received uniform illumination for 15 min and the optical density was then measured spectrophotometerically at 560 nm. One unit of enzyme activity was defined as the amount of enzyme giving 50% inhibition of reduction of NBT and expressed as U/mg protein. Enzymatic activity was calculated from inhibition of reduction of NBT using standard curve constructed by varying amount of the test samples.

2.7 Determination of Catalase (CAT) Activity

The CAT activity was determined by method of Aebi [24]. 10 µl of absolute ethanol is added to 100 µl of tissue extract (20–30 µg protein) and placed in an ice bath for 30 min. 9 volumes of 1% Triton X100 (900 µl) were added to the mixture and then homogenized. The sample (100 µl) was then mixed with 500 µl of 66 mM of hydrogen peroxide and 400 µl of 50 mM phosphate buffer (pH 7.0) containing 1mM EDTA and the absorbance was monitored at 240 nm spectrophotometerically. One unit of CAT activity was defined as 1 nmol of hydrogen peroxide degraded/minute/mg protein.

2.8 Determination of Glutathione Peroxidase (Gpx) Activity

The activity of GPx in kidney tissues was determined based on the utilization of reduced GSH by the enzyme [23]. The kidney tissue homogenate (100 µl) was treated with 100 µl of GSH, 2.1 µl of buffer, 100 µl of sodium azide and 1.2 mM hydrogen peroxide (100 µl). The mixture was incubated at 37°C for 6 min and 2 ml of phosphoric acid (1.67%) were added and centrifuged. To the supernatant (2 ml), 1 ml of disodium hydrogen phosphate and 1 ml of DTNB were added and incubated at 37°C for 10 min. The absorbance was read at 412 nm spectrophotometerically.

2.9 Determination of Glutathione (GSH) Content

GSH level in kidney tissues was determined by the method of Beutler and Kelly [25]. GSH was measured by its reaction with 5,5'-dithionitrobenzoic acid (DTNB). For the reactions, 0.125 ml of 25% (w/v) trichloroacetic acid solution (TCA) was added to 0.5 ml of kidney tissue homogenate. The tubes were placed on ice for 5 min and then further diluted with 0.6 ml of 5% TCA. Each sample was then centrifuged (5000 rpm, 4°C, 10 min) and the resultant supernatant was taken for GSH estimation. A volume of aliquot (0.3 ml) was combined with 0.7 ml of 0.2 M phosphate buffer, and then 2 ml of 0.6 mM DTNB was added to the tubes and the intensity of the resulting yellow color was measured at 412 nm spectrophotometerically. Values were expressed as nmol/mg protein.

2.10 Measurement of Lipid Peroxidation (LPO) Level

The kidney tissue homogenate (0.1 ml) was treated with 200 µl of sodium dodecyl sulfate (SDS-8%) and 1.5 ml thiobarbutric acid (TBA). The mixture was kept in water bath for 1 h at room temperature and cooled by adding 1 ml of distilled water followed by 5 ml of a mixture of *n*-butanol and pyridine (15: 1, v/v) and centrifuged. The supernatant was taken and the optimal intensity at 532 nm was measured spectrophotometerically. The levels of LPO were expressed as nmol/mg protein [26]. The protein level was estimated by the Lowry method [27].

2.11 Measurement of Tissue TNF-α Level

TNF-α concentration in kidney tissues was measured in triplicate by using a Mouse Cytokine Lincoplex kit (Linco Research, Inc., St Charles, MO, USA).

2.12 Statistical Analysis

Data are presented as means± SD .Statistical analysis were done using one-way analysis of variance (ANOVA) followed by Tukey test, except necrotic scoring was done using chi-square test, (SPSS version17). $P \leq 0.05$ was considered as significant.

3. RESULTS

3.1 Effect of Sitagliptin on Cisplatin-induced Renal Dysfunction

The levels of traditional indicators of kidney damage (BUN and creatinine) were measured. Cisplatin treatment significantly increased the levels of BUN and serum creatinine compared to the control group ($P < 0.01$) as shown in Table 1. Cisplatin-treated mice with sitagliptin noticeably alleviated the elevated levels of BUN and serum creatinine from 84.45±0.16 to 43.48±0.12 mg/dL ($P < 0.01$) and from 1.74±0.03 to 1.13±0.009 mg/dL ($P < 0.01$), respectively. Sitagliptin alone did not exhibit any effect on BUN and creatinine levels.

3.2 Effect of Sitagliptin on Renal SOD Activity Measured in Cisplatin-induced Nephrotoxicity in Mice

Fig. 1(a) shows that treatment with sitagliptin increased renal SOD activity level (13.36±0.21 U/mg protein) ,when compared to level of cisplatin-induced nephrotoxicity (7.05 ± 0.25 U/mg protein) (Group 2). The treatment with sitagliptin alone did not affect renal SOD level (13.15 ± 0.15 U/mg protein) (Group 3) when compared to the control group (13.86 ± 0.18 U/mg proteins) (Group 1).

3.3 Effect of Sitagliptin on Renal CAT Activity Measured in Cisplatin-induced Nephrotoxicity in Mice

Fig. 1(a) shows that treatment with sitagliptin significantly ($P < 0.001$) increased renal CAT level (30.55± 0.11 nmol/mg protein) (Group 4) compared to cisplatin-induced group (20.24± 0.12 nmol/mg protein) (Group 2). However, sitagliptin alone did not affect renal CAT level (35.26±0.18 nmol/mg protein) (Group 3) in comparison to the control group (35.33± 0.22 nmol/mg protein) (Group 1).

3.4 Effect of Sitagliptin on Renal GSH Activity Measured in Cisplatin-induced Nephrotoxicity in Mice

Fig. 1(b) also shows that treatment with sitagliptin significantly ($P < 0.01$) increased the level of GSH of kidney tissue (40.33 ± 0.13 nmol/mg protein) (Group 4) when compared to the level of cisplatin group (25.32 ± 0.19 nmol/mg protein) (Group 2). However, sitagliptin alone did not affect GSH activity in comparison to the control group (45.33 ± 0.18 nmol/mg protein) (Group 1).

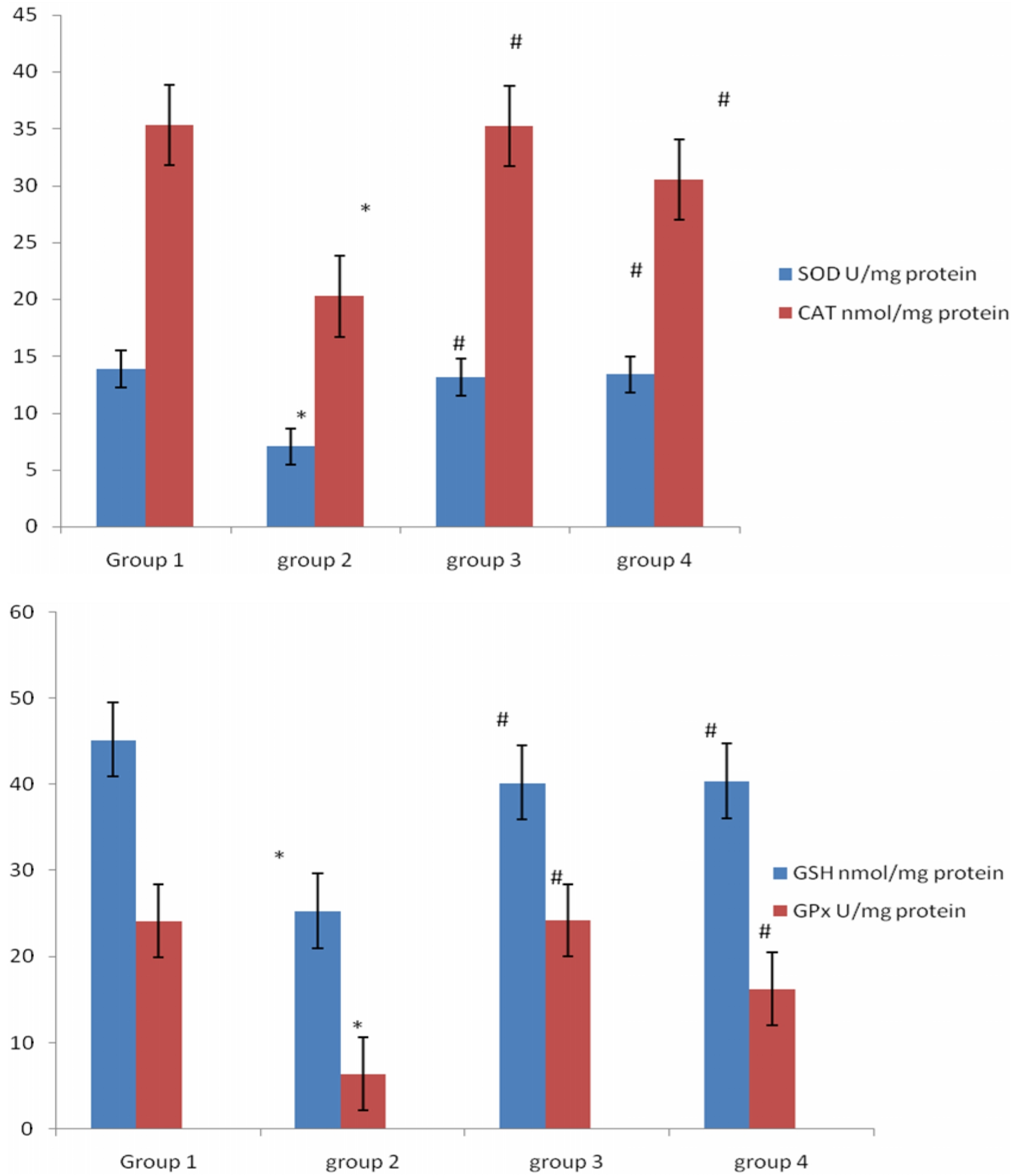

Fig. 1(a,b). Effect of sitagliptin on renal superoxide dismutase(SOD) (U/mg protein), catalase (CAT) (nmol/mg protein) ,glutathione (GSH)(nmol/mg protein), and glutathione peroxidase(GPx)(U/mg protein) in cisplatin induced nephrotoxicity in mice. Data (mean±SD) (n=12 in each group)

**P<0.01 versus control group, # P<0.01 versus cisplatin treated group*

3.5 Effect of Sitagliptin on Renal Gpx Activity Measured in Cisplatin-induced Nephrotoxicity in Mice

Fig. 1(b) presents that treatment with sitagliptin significantly ($P < 0.01$) increased renal GPx level (16.27 ± 0.08 U/mg protein) (Group 4) when compared to the level of cisplatin group (6.40 ± 0.15 U/mg protein) (Group 2). However, sitagliptin alone did not affect GPx activity (24.20 ± 0.09nmol/mg protein) (Group 3) in comparison to the control group (24.17± 0.11 nmol/mg protein) (Group 1).

3.6 Effect of Sitagliptin on Renal LPO Activity Measured in Cisplatin-induced Nephrotoxicity in Mice

Fig. 2 shows that treatment with sitagliptin significantly ($P < 0.01$) decreased the level of renal LPO level (0.87 ± 0.01 nmol/mg protein) (Group 4) when compared to the level of cisplatin group (1.87 ± 0.03 nmol/mg protein) (Group 2). However, sitagliptin alone did not affect renal LPO level (0.63 ± 0.02nmol/mg protein) (Group 3) in comparison to the control group (0.62 ± 0.02 nmol/mg protein) (Group 1).

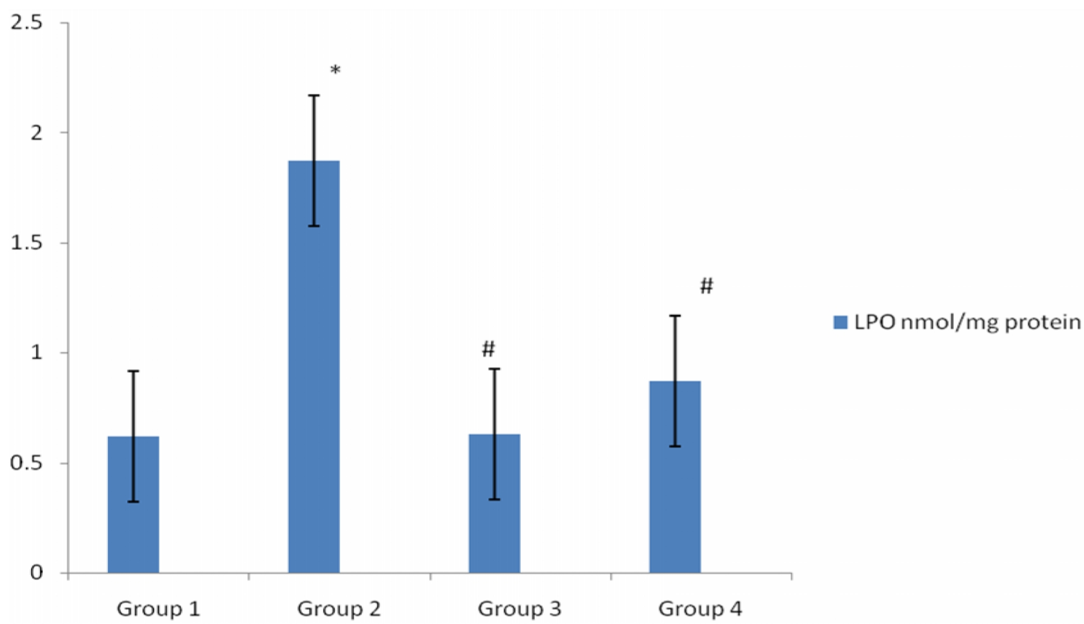

Fig. 2. Effect of sitagliptin on renal lipid peroxidation products (LPO) (nmol/mg protein) in cisplatin induced nephrotoxicity in mice. Data (mean±SD) (n=12 in each group)

**P<0.01 versus control group, # P<0.01 versus cisplatin treated group*

3.7 Effect of Sitagliptin on Renal TNF-α Level Measured in Cisplatin-induced Nephrotoxicity in Mice

Fig. 3 shows that treatment with sitagliptin significantly ($p < 0.01$) decreased the level of renal TNF-*α* level (60.77 ± 0.01 nmol/mg protein) (Group 4) when compared to the level of cisplatin group (250.44 ± 0.16 Ug/mg protein) (Group 2). However, sitagliptin alone did not affect renal TNF-*α* level (50.63 ± 0.14Ug/mg protein) (Group 3) in comparison to normal control group (50.35± 0.14 Ug/mg protein) (Group 1).

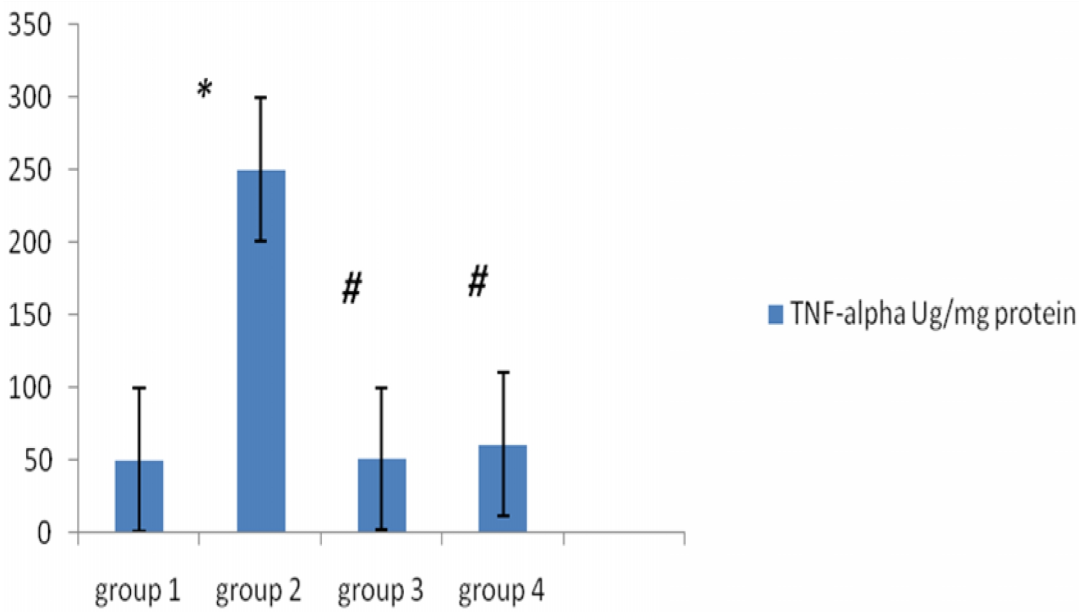

Fig. 3. Effect of sitagliptin on renal TNF-α (ug/mg protein) in cisplatin induced nephrotoxicity in mice Data (mean±SD) (n=12 in each group)
**P<0.01 versus control group, # P<0.01versus cisplatin treated group*

3.8 Effect of Sitagliptin on Renal Histopathology and Tubular Necrosis in Cisplatin-induced Nephrotoxicity in Mice

Fig. 4 presents Histopatholgical changes in kidney tissue of cisplatin treated group were showing necrotic debris and proteniceous effusion which ameliorated with sitagliptin treatment.

Fig. 5 presents a semi-quantitative measure of tubular necrosis. Cisplatin produced a large increase in necrosis and the treatment with sitagliptin ameliorated cell necrosis in cisplatin group.

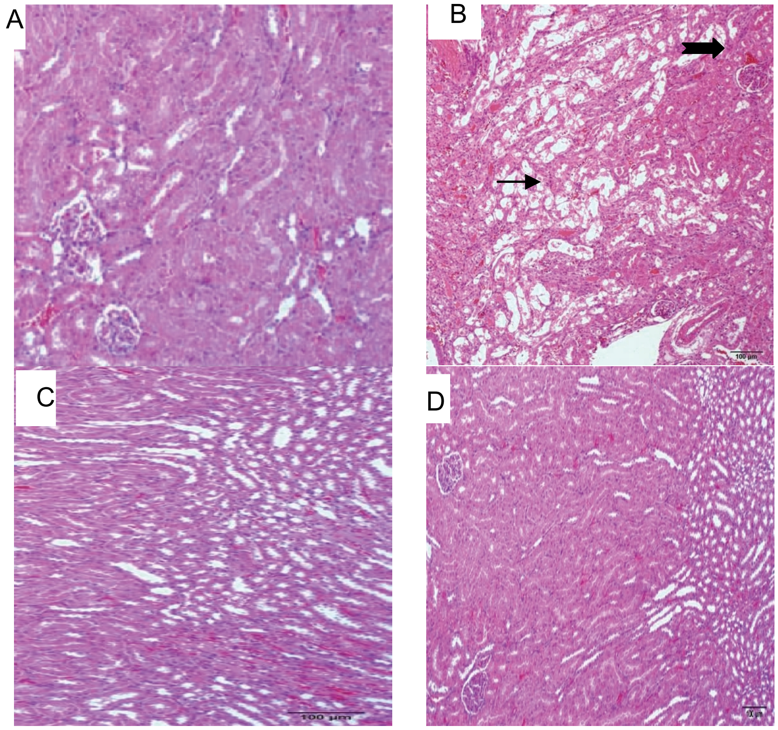

Fig. 4. The kidney histological changes induced by cisplatin in mice: (a) control mice; (b) cisplatin-treated mice; (c) sitagliptin –treated mice; and (d) sitagliptin +cisplatin treated mice. Thick arrow indicates necrotic debris, and thin arrows indicate proteinaceous effusion

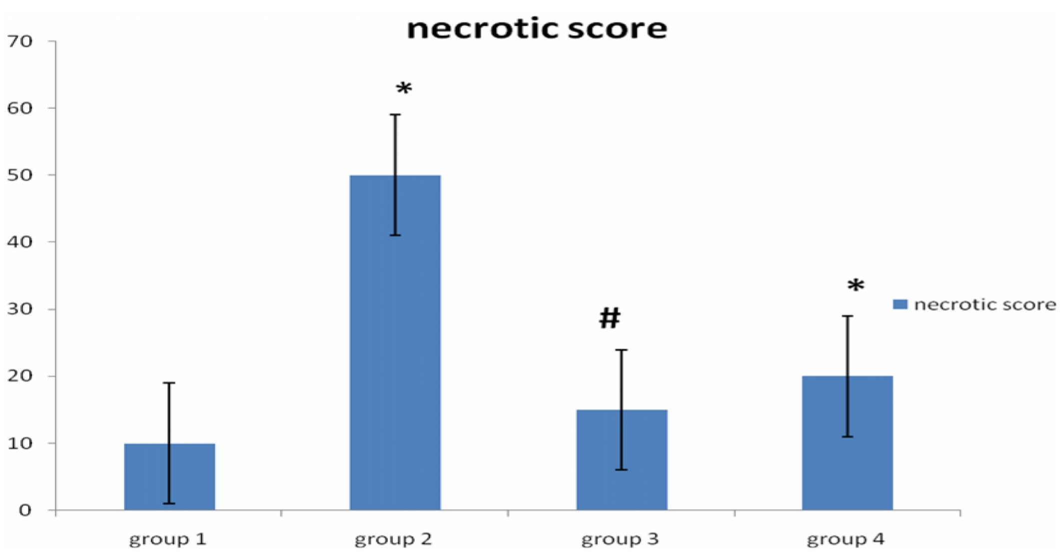

Fig. 5. Effect of sitagliptin on necrotic score in cisplatin induced nephrotoxicity in mice.Data (mean±SD) (n=12 in each group)
**P<0.01 versus control group, # P<0.01 versus cisplatin treated group*

4. DISCUSSION

In the present work, cisplatin induced increased oxidative stress which is presented by increased levels of total lipid peroxidation, associated with decreased SOD, GPx, GSH and CAT levels. The acute nephrotoxic effect of cisplatin is described by many studies. CDDP anti-cancer action is due to the conversion to a di-ucl-acquocomplex that produces an interstrand cross-link with double-strand DNA, resulting in DNA synthesis. The most popular deleterious effect preventing the efficacy of CDDP is nephrotoxicity which starts in the S3 segment of the proximal convoluted tubule. It has been established that, depletion of sulfhydryl (SH) groups, impaired anti-oxidant defense system and mitochondrial dysfunction in proximal renal tubules may be the causes of CDDP drug to induce renal lesion [28].

Total lipid peroxidation and oxidative free radicles are involved in acute renal failure that is clinically in the form of reduction in glomerular filtration rate, fall in renal blood flow, decrease in the urinary concentrating ability, as well as changes in urine volume, creatinine clearance and GSH status [29-31] .

There is evidence that CDDP induces remarkable activation of renal NF-κB. NF-κB activity in the kidney, is the link between inflammation and oxidative stress, that both are related to each other and leading to a vicious circle [32]. Several anti-oxidants such as alpha - lipoic acid and thymoquinone have been investigated to protect kidney against cisplatin-induced nephrotoxicity experimentally [33].

The hypothesis of this work is based on that the inhibition of NF-κB mediated TNFα activation, is capable of attenuating CDDP-induced renal injury .So the renal protective mechanism of sitagliptin against cisplatin-induced nephrotoxicity had been investigated.

Sitagliptin, is a highly selective DPP 4 inhibitor, leading to preservation of GLP-1. The protein encoded by the *DPP4* gene, is an enzyme expressed on the surface of most cells and is responsible for immune regulation, signal transduction , apoptosis, suppression of tumours and glucose metabolism [11].

Liu et al. [34] described the inhibitory effect of GLP-1 on TNFα mediated endothelial dysfunction. GLP-1, has a renoprotective role in ischemia-reperfusion injury in experimental models, and GLP-1 agonists exerts a renoprotective effect in diabetic nephropathy and cisplatin induced renal toxicity [14,15,35].

Renal protective effects of GLP-1 receptor agonists, have been established in either chronic renal failure and or acute kidney injury and this renal effect may be beyond their glucose-lowering effect [36].

Kodera et al. [32] found that exendin-4 (GLP-1 receptor agonist) decreases albuminuria, glomerular hyperfiltration, glomerular hypertrophy and mesangial matrix expansion in the diabetic rats with no effect on neither changing blood pressure nor body weight. Exendin-4 also inhibits macrophage infiltration, and decreases protein levels of intercellular adhesion molecule-1 (ICAM-1) and type IV collagen, associated with decreasing oxidative stress and nuclear factor-κB activation in renal tissue. In addition, he found that the GLP-1 receptor is produced on monocytes/macrophages and glomerular endothelial cells. Kodera in vitro study, concluded that exendin-4 acts by direct action on the GLP-1 receptor, and prevents pro-inflammatory cytokines flow from macrophages and ICAM-1 presence on glomerular endothelial cells.

The anti-inflammatory effect of GLP-1 agonists are shown in different pathological conditions as atherosclerosis [37], obesity related insulin resistance, chronic renal insufficiency and cardio renal syndrome [38-41].

Each individual GLP-1 agonist may not be suitable for this indication, because of its own different kinetics, For example, exenatide is eliminated by renal route, should not be given in renal failure and may lead to ischemic renal failure [36].

Elimination of sitagliptin is through renal active tubular secretion and it does not need dose adjustement in mild to moderate renal failure. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), that is reponsible for its renal elimination and has no clinical significant effect . Sitagliptin is also a substrate of p-glycoprotein, which mediates the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, does not reduce the renal clearance of sitagliptin [42].

On the other hand, cisplatin could induce over expression of p-glycoprotein and its renal uptake is via organic cation transporters (OCTs) and organic anion transporter 5 (Oat5) that is a potential biomarker of cisplatin nephrotoxicity [43-45]. So, from other studies and the present work, it seems that there is no harmful interaction, on administration our investigated drugs together .

5. CONCLUSION

The present study shows that the acute nephrotoxic effect of cisplatin in a mouse model could be ameliorated using the antioxidant & anti-inflammatory protective effects of sitagliptin However, their interaction either at a kinetic and or a dynamic levels needs further evaluation.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors have declared that all experiments have been examined and approved by our local ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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