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Effect of Saxagliptin on Cisplatin-Induced Nephrotoxicity in Rats

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Abstract:

Background: Nephrotoxicity is the most common side effect of cisplatin, cisplatin as a chemotherapy is used widely in the treatment of solid tumors so nephro-protection is highly recommended. Saxagliptin is a new antidiabetic drug that show great effect in improving the glycemic profile of patient with type 2 diabetes mellitus. **Aim**: The current study investigated the renoprotective effect of saxagliptin (12.5mg/kg, IP) against cisplatin-induced nephrotoxicity in rats. **Methods**: Twenty-four adult male albino rats were randomly assigned to four groups, each group contained 6 rats. **Results**: Saxagliptin administration for 14 days revealed a significant nephroprotection against cisplatin-induced nephrotoxicity manifested by improvement in kidney function, significant decrease in the serum urea and creatinine, albuminuria, and albumin/creatinine ratio, while significant increase in the urine volume, and urine creatinine. Also, kidney contents of MDA, TNFα and DPP4 enzyme level significantly declined with significant increase in GSH, catalase concentration compared to cisplatin treated group. Also, significant histopathological improvement occurred. **Conclusion:** saxagliptin has anti oxidative stress effects and anti-inflammatory properties through long-lasting inhibition of renal membrane bound DPP4 enzyme.

Keywords: Saxagliptin; Cisplatin; Nephrotoxicity; Nephroprotection, catalase, Reduced glutathione, Malondialdehyde, DPP4 enzyme, TNF alpha, Histopathology.

1-Introduction:

Nephrotoxicity can be defined as the adverse effect of substances on renal function leading to the development of functional or structural kidney damage after exposure to

one or more of a wide variety of drugs, or toxins (1).

Cisplatin is one of the most potent antineoplastic agents used to treat a wide assortment of solid tumors. However, nephrotoxicity is a major adverse effect after cisplatin administration (2).

Cisplatin-induced nephrotoxicity occurs through apoptosis and necrosis (3), vascular factors, and inflammation of the tubules (4), oxidative stress (5,6). The reactive oxygen species (ROS) and reactive nitrogen species (RNS) production alter the structure and function of cellular membranes (7).

Their accumulation in kidney and lysosomes (8) explained the mechanisms for cisplatin-induced acute nephropathy (9). Therefore, the free radical scavengers and the antioxidants agents can prevent cisplatin induced nephrotoxicity.

There is no effective pharmacological intervention for cisplatin induced nephrotoxicity. Many investigators have focused on protective and therapeutic interventions that might modify or minimize this process.

Saxagliptin is a member of the Dipeptidyl peptidase-4 (DPP4) inhibitors. They are a class of drugs used for management of T2DM. They function mainly by inhibiting the enzyme responsible for the breakdown of glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), prolonging the half-life of endogenous GLP-1 and GIP, with enhanced glucose-dependent insulin secretion and decreased glucose-dependent glucagon secretion (10,11).

In addition to an incretin action of DPP-4 inhibitors, DPP-4 inhibitors could induce the pleiotropic actions such as anti - inflammatory, anti-fibrotic and antioxidant effects (12).

It has been reported that saxagliptin exerted reno-protective effects through its tight covalent binding and long-lasting inhibition of renal membrane -bound DPP4 compared to other members of DDP4 inhibitors (13).

The aim of the present study is to evaluate the reno-protective effects of saxagliptin on cisplatin induced nephrotoxicity in rats and the role of inhibiting inflammation, oxidative stress and DPP4 enzyme activity in cisplatin-induced nephrotoxicity.

2- Materials and Methods:

A) Materials

Drugs:

1- Saxagliptin (Onglyza): 5 mg tablets from (Bristol-Mayers, Pennington, NJ, USA).

2- Cisplatin: vial each 50ml vial contains 50mg cisplatin (i.e.1 mg/ml).

from MYLAN S.A.S-FRANCE RAMCO.

Chemicals:

1- NaCl 0.9%: from AL MOTTAHEDOON PHARMA, 10th of Ramadan, Egypt.

2- Tween (80): from EL Nasr Pharmaceutical Chemicals, Gesr El Suez, Egypt.

Stains:

Hematoxylin and Eosin.

Kits:

1- Urea Kit
2- Creatinine Kit
3- Albumin Kit
4- Reduced Glutathione (GSH) Kit
5- Malondialdehyde (MDA) Kit
6- Catalase Kit

All are colorimetric and obtained from (Bio diagnostic, Badr City, Egypt)

7- Dipeptidyl peptidase Ⅳ ELISA Kit obtained from (My BioSource, Vancouver, British Columbia).
8- TNF alpha ELISA Kit obtained from (Ray Biotech 3607 Parkway Lane, Suite 100 Norcross, GA 30092).

Animals:

Twenty four adult male albino rats, matched for age (3- 4 months) and weight (150-250g) were used. The animals were handled according to the guidelines of the local ethical committee, approval number 019-66 which comply with the international laws for the use and care of laboratory animals. Rats bred in the animal house of Nahda Beni-Suef University. They were caged individually in fully ventilated room at fixed room temperature (21± 2^{o}c), exposed to natural daily light/ dark cycle, fed with standard laboratory diet and allowed to water add libitum. They were acclimatized for 2 weeks before randomly allocated to 4 groups.

B) Methods:

Experimental Design:

The rats were randomly assigned to four groups. Each group contained 6 rats.

Group (1) Normal control group: rats received 0.9% NaCl in tween 80 I.P for 14 days.

Group (2) Saxagliptin treated group: normal rats received saxagliptin (12.5mg/kg) in tween 80 daily IP for 14 days (14).

Group (3) Cisplatin treated group: rats received cisplatin on 8th day (5 mg /kg, IP single injection) (15). This group serves as a model of cisplatin induced nephrotoxicity.

Group (4) Saxagliptin and Cisplatin treated group: rats received saxagliptin by the same previous dose, and route of administration 7days before and 7 days after IP single injection of cisplatin administration. Cisplatin was given by the same previous dose. Rats were sacrificed after the 7^{th} day from cisplatin intake.

Cisplatin induced nephrotoxicity in rats

On the 8^{th} day of the experiment, nephrotoxicity was induced by single IP injection of 5mg/Kg of cisplatin according to the weight of each rat (15).

Saxagliptin was injected daily 12.5mg/kg IP for 7 days before and 7 days after cisplatin single IP injection.

Determination of the body weight of each rat:

Body weights of the rats used in different groups were determined at the start and at the end of the experiment. The percentage of changes in body weights were calculated.

On the 14th day of the experiment, animals were caged at metabolic cages for 24hrs for urine collection. On the 15th day of the experiment, urine samples were collected for estimation of:

1- Urine volume.
2- Urine albumin.
3- Urine creatinine.
4- Albumin/ creatinine ratio.

-Venous blood samples were withdrawn from the retro-orbital plexus of all the animals at the end of experiment and micro capillary tubes were used (16).

Up to 4 ml of sample was obtained and then samples were left to cool 15 min for clotting for proper separation of serum. The blood samples were centrifuged at 1500 rpm for 15 minutes for separation of serum. Then the serum was transferred into clean vials and stored at -20ºC in a freezer (17) for measurement of

1- Urea nitrogen.
2- Creatinine.

All rats were sacrificed by decapitation and dissected after administration of ethyl ether inhalation anesthesia. Both kidneys were removed for biochemical and histopathological tests. All approved conditions used for animal housing and handling were considered.

Estimation of the weights of both kidneys

At the end of the experiment, the weights of both kidneys (absolute weight) and the relative kidney weights were calculated to evaluate the effect of different drugs on each kidney weight.

Relative kidney weight= absolute kidney weight (gm)/bodyweight (gm)x 100.

Preparation of kidneys

- The left kidney tissue of the animals in all the groups were subjected to homogenization, and measurement of the following biochemical parameters:
  1- Malondialdehyde (MDA).
  2- Reduced Glutathione.
  3- Catalase.
  4- DPP-4 enzyme.
  5- TNF alpha.
- The right kidney tissue of the animals in all the groups was subjected to histopathological examination.

Statistical analysis

Data were expressed for each parameter investigated as a mean ± standard deviation of the mean (SD). Analysis of variance one way (ANOVA) was used to compare the different groups followed by Tukey-Kramer for post hoc test. All statistics were carried out using SPSS package (Statistical Package for Social Sciences) version 22. Differences were considered statistically significant when the p value is < 0.05.

3- Results:

A) Weight results 1-The effects of saxagliptin on the percentage of changes in body weights and the kidney weights

In the current study there was a statistically significant difference between the studied groups regarding the percent of change of body weight .Among the control group there was a percent of increase with median 31.4% versus percent of decrease 7.6% among the cisplatin group, 7% in the saxagliptin group and 15.8% among the treated group with .There was no statistically significant difference between the cisplatin, saxagliptin and the treated group(**table 1**).

As regards the weights of both kidneys at the end of experiment, the current study showed no significant changes in the relative weights of both kidneys in the cisplatin-treated group compared to the normal control group. On the other hand, a significant increase is observed in the absolute weights of both kidneys in cisplatin-treated group compared to the normal control group. This increase was significantly ameliorated when cisplatin group is treated with saxagliptin (**table 1**).

Table (1) The effects of treatment on the percentage of change in the body weights and absolute and relative weights of both kidneys of cisplatin- induced nephrotoxicity rats at the end of experiment.

	Absolute kidney weight (gm)	**Relative kidney weight (gm)**	**% of change of body weight Mean±SD Median (IQR)**
Normal control	1.82±0.10	0.83±0.09	28.7±7.5 -31.4 (-34 to- 20.8)
Saxagliptin	1.61±0.17	0.88±0.22	0.22±19.4 7 (-19.8 to -13.5)
Cisplatin	2.34±0.12[a]	1.05±0.09	6.4±4.5 7.6(1.7 to 9.8)
Cisplatin+Saxagliptin	1.71±0.19[b]	0.98±0.11	11.6±13.5 15.8 (-2.7 to -21.7)

Data are expressed as (Mean ± SD) (n=6).

(a) Significantly different from the normal control group values (p value <0.05).

(b) Significantly different from the cisplatin-treated group values (p value <0.05).

B) Biochemical results:

I-Biochemical results in the kidney tissue homogenate

A-The effect of saxagliptin on oxidative stress markers

The current study showed that the renal tissue content of GSH and catalase activity decreased significantly in the cisplatin-treated group compared to the normal control group. On the other hand, the cisplatin significantly increased the MDA level compared to normal control group. Cisplatin group pretreated with saxagliptin revealed significant alleviation of these changes compared to the cisplatin treated group but still significant difference compared to the normal control group values. Interestingly, even the normal group pretreated with saxagliptin showed a significant elevation of the GSH level compared to the normal control group (**table 2**).

Table (2): The effect of saxagliptin on levels of reduced glutathione (GSH) (µmol/gm tissue), malondialdehyde (MDA) (nmol/gm tissue) and catalase (CAT) (U/gm tissue) in kidney tissues of cisplatin-induced nephrotoxicity in rats.

	GSH (µmol/gm tissue)	**MDA (nmol/gm tissue)**	**CAT (U/gm tissue)**
Normal control	77.06 ± 2.80	28.26 ± 2.16	141.06 ± 14.05
Saxagliptin	88.04 ± 3.84[a]	20.76 ± 5.12	150.26 ± 13.88
Cisplatin	42.52 ± 8.23 [a]	105.40 ± 9.52[a]	75.10 ± 9.32 [a]
Cisplatin+Saxagliptin	69.44 ± 2.85[ab]	55.08 ± 9.65[ab]	120.48 ± 2.44[ab]

Data are expressed as (Mean ± SD) (n=6).

(a) Significantly different from the normal control group values (p value <0.05).

(b) Significantly different from the cisplatin-treated group values (p value <0.05).

B-The effect of saxagliptin on inflammatory marker (TNFα) and DPP4 enzyme level:

The current study showed that the renal tissue content of TNFα increased significantly in the cisplatin -treated group compared to the normal control group. Cisplatin group pretreated with saxagliptin revealed a significant alleviation of this increase compared to the cisplatin group value but significant difference still present compared to the normal control group. Also, the normal control group pretreated with saxagliptin showed a significant decrease of the TNFα level compared to the normal control group. As regards DPP4 enzyme, the current study showed that the renal tissue content of DPP4 enzyme increased significantly in the cisplatin- treated group compared to the normal control group. Cisplatin group pretreated with saxagliptin revealed a significant reduction of this increase level of DPP4 enzyme compared to the cisplatin-treated group value but significant difference is still present compared to the normal control group. Also, the normal control group pretreated with saxagliptin showed significant decrease of the DPP 4 level compared to the normal control group (**table 3**).

Table (3): The effect of saxagliptin on the level of TNFα (pg/gm tissue) and on DPP4 enzyme (ngm/mg protein) in kidney tissues of cisplatin-induced nephrotoxicity in rats.

	TNFα (pg/gm tissue)	**DPP4 enzyme (ngm/mg protein)**
Normal control	17.16 ± 2.648	1.69 ± 0.25
Saxagliptin	13.64 ± 0.873 [a]	1.32 ± 0.18[a]
Cisplatin	94.34 ± 12.816[a]	7.12 ± 0.73 [a]
Cisplatin+Saxagliptin	60.76 ± 7.944[ab]	3.96 ± 0.25 [ab]

Data are expressed as (Mean ± SD) (n=6).

(a) Significantly different from the normal control group values (p value <0.05).

(b) Significantly different from the cisplatin-treated group values (p value <0.05).

II-Biochemical results in urine.

The current study showed that urinary level of albumin and albumin / creatinine ratio increase significantly in the cisplatin-treated group compared to the normal control group. Also, cisplatin significantly decreased the urine volume and urinary creatinine compared to normal control group. Cisplatin group pretreated with saxagliptin revealed a significant alleviation of these changes compared to the cisplatin group values but significant difference is still present when compared to the normal control group. Interestingly, even the normal group pretreated with saxagliptin showed significant increase in the urinary creatinine compared to the normal control group (**table4**).

Table (4): The effect of saxagliptin on urine volume (ml), Urine albumin(mg/dl), Urine creatinine (gm/dl) and Albumin /creatinine ratio(mg/gm) in cisplatin induced nephrotoxicity rats.

	Urine volume(ml)	**Urine albumin (mg/dl)**	**Urine creatinine (gm/dl)**	**Albumin/creatinine ratio(mg/gm)**
Normal control	4.16 ± 0.38	0.05 ± 0.08	0.34±0.01	1.58 ± 0.63
Saxagliptin	4.34 ± 0.19	0.43 ± 0.13	0.53 ± 0.06[a]	0.84 ± 0.31
Cisplatin	1.8 ± 0.54 [a]	3.45 ± 0.65 [a]	0.05 ± 0.02 [a]	76.74 ± 31.49 [a]
Cisplatin+Saxagliptin	3.66 ± 0.19[ab]	1.04 ± 0.15 [ab]	0.20 ± 0.03[ab]	5.18 ± 0.74[ab]

Data are expressed as (Mean ± SD) (n=6).

(a) Significantly different from the normal control group values (p value <0.05).

(b) Significantly different from the cisplatin-treated group values (p value <0.05)

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III-Biochemical results in serum.

The current study showed significantly impaired renal functions as manifested by significant increase in the serum urea and creatinine in the cisplatin-treated group compared to the normal control group. This increase was significantly ameliorated when cisplatin group is treated with saxagliptin but significant difference is still present when compared to the normal control group (**table 5**).

Table (5): The effect of saxagliptin on serum urea (mg/dl) and creatinine (mg/dl) in cisplatin induced nephrotoxicity rats.

	Urea(mg/dl)	**Creatinine(mg/dl)**
Normal control	45.60 ± 7.10	0.18 ± 0.04
Saxagliptin	91.40 ± 7.70	0.18± 0.05
Cisplatin	4.66 ± 8.40[a]	0.92 ± 0.19[a]
Cisplatin+Saxagliptin	57.26 ± 3.40[ab]	0.44 ± 0.10[ab]

Data are expressed as (Mean ± SD) (n=6).

(a) Significantly different from the normal control group values (p value <0.05).

(b) Significantly different from the cisplatin-treated group values (p value <0.05).

C- The effect of tested drugs on histopathology of the right kidney of all rats in all groups at the end of experiment.

Histopathological study of a section in the right kidney of rats in the normal control group showed normal renal tissue with normal glomeruli formed of capillary tuft surrounded by Bowman's capsule, proximal convoluted tubules with narrow lumen lined by high cuboidal cells with homogeneous eosinophilic cytoplasm and distal convoluted tubules with wide lumen lined by low cuboidal cells with no signs of inflammation or necrosis(**figure:1A**).

Giving saxagliptin for 14 days showed unremarkable histopathological changes (**figure:1B**).

Induction of nephrotoxicity in rats resulted in acute tubular injury consist of dilated renal tubules with marked hydropic degeneration with increased cytoplasmic vacuolization, associated with dilated congested interstitial

capillaries with extravasation of RBCS. Some of tubular epithelial cells showed pyknotic small dark sloughed nuclei (**figure:2A**). In addition, there was glomerular atrophy associated with dilated congested cortical capillaries with moderated interstitial edema & extravasated RBCS (**figure:2B**). Furthermore there was acute renal tubular necrosis associated with interstitial moderate chronic inflammatory cells infiltration and extravasation of RBCS, increase tissue interstitium indicating marked tubular damage, tubular dilatation with intraluminal sloughing of the lining epithelial cells with pyknotic nuceli and karolysis **(figure:2 C ,D,E**).

Treatment of rats with nephrotoxicity with saxagliptin resulted in decrease congestion, also tubular degenerative and interstitial inflammatory changes generally were significantly reduced, the capillary glomerular tuft became slightly normal with absence of interstitial inflammatory cells (**figure:3A, B).**

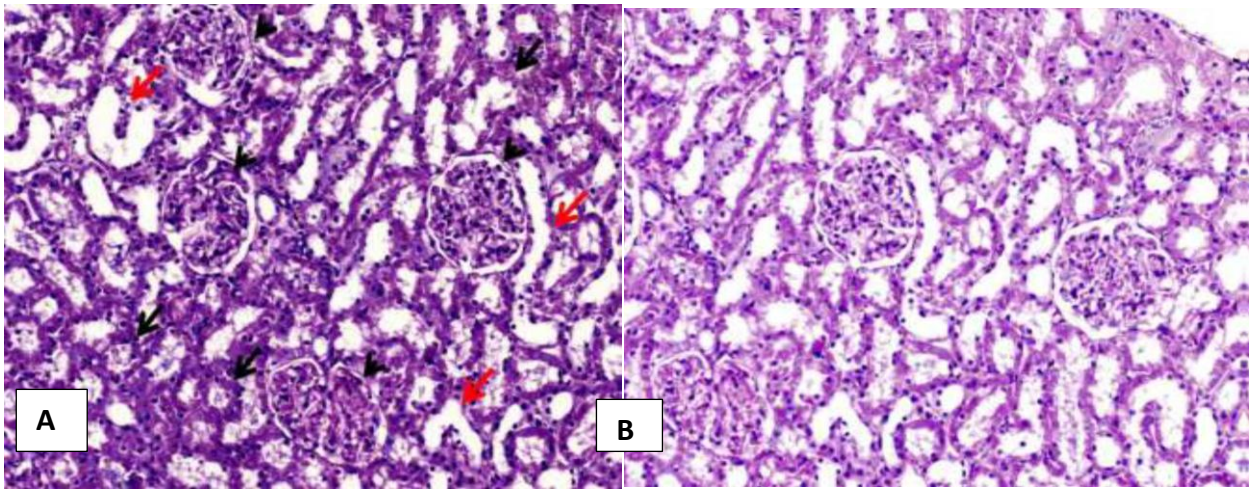

Fig. 1. Histopathological changes in the right kidney of all rats in normal control group(A) and saxagliptin treated group(B) at the end of experiment.

A: showing normal glomeruli formed of capillary tuft surrounded by Bowman's capsule (arrows head), proximal convoluted tubules with narrow lumen lined by high cuboidal cells with homogeneous eosinophilic cytoplasm (black arrows) and distal convoluted tubules with wide lumen lined by low cuboidal cells (red arrows). (H&E stain ×200).

B: Light microscopy of renal section from saxagliptin group, renal tissue demonstrated unremarkable histopathological changes. (H&E stain ×200).

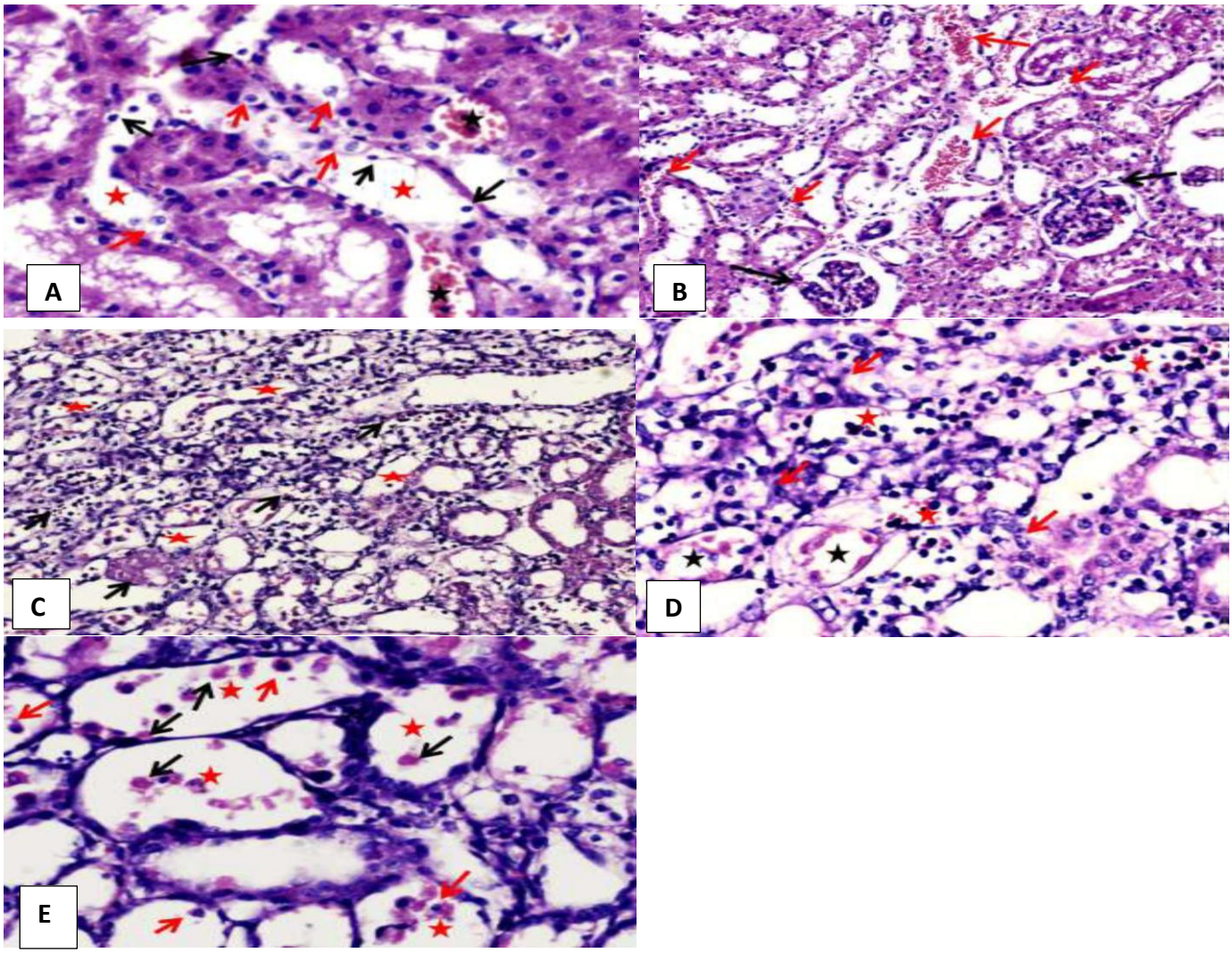

Fig. 2. Histopathological changes in the right kidney of all rats in cisplatin treated group at the end of experiment.

A: Light microscopy of renal section from diseased group demonstrated diffuse acute renal tubules injury consist of dilated renal tubular (red star) with marked hydropic degeneration with increased cytoplasmic vacuolization (red arrows), associated with dilated congested interstitial capillaries with extravasation RBCS (black star) , some of tubular epithelial cells showed pyknotic small dark nuclei and sloughed (black arrows) (H&E stain ×400).**B**: Light microscopy of renal section from diseased group demonstrated glomerular atrophy (black arrow) associated with dilated congested cortical capillaries with moderated interstitial edema & extravasated RBCS (red arrows) (H&E stain ×200).**C**: Light microscopy of renal section from diseased group demonstrated diffuse acute renal tubules necrosis associated with interstitial moderate chronic Inflammatory cells infiltration and extravasation of RBCS after administration of cisplatin (H&E stain ×100). **D**: Light microscopy of renal section from diseased group demonstrated acute renal tubules necrosis (black stars) associated with interstitial moderate chronic inflammatory cells infiltration and extravasation of RBCS (red stars), increase tissue in interstitium indicating marked tubular damage (red arrows) (H&E stain ×200).**E**: Light microscopy of renal section from diseased group demonstrated acute renal tubular necrosis of proximal convoluted tubules consisted of marked tubular dilatation with intraluminal sloughing of the lining epithelial cells (red stars), cells with pyknotic nuceli (red arrows) & karolysis (black arrows) (H&E stain ×400).

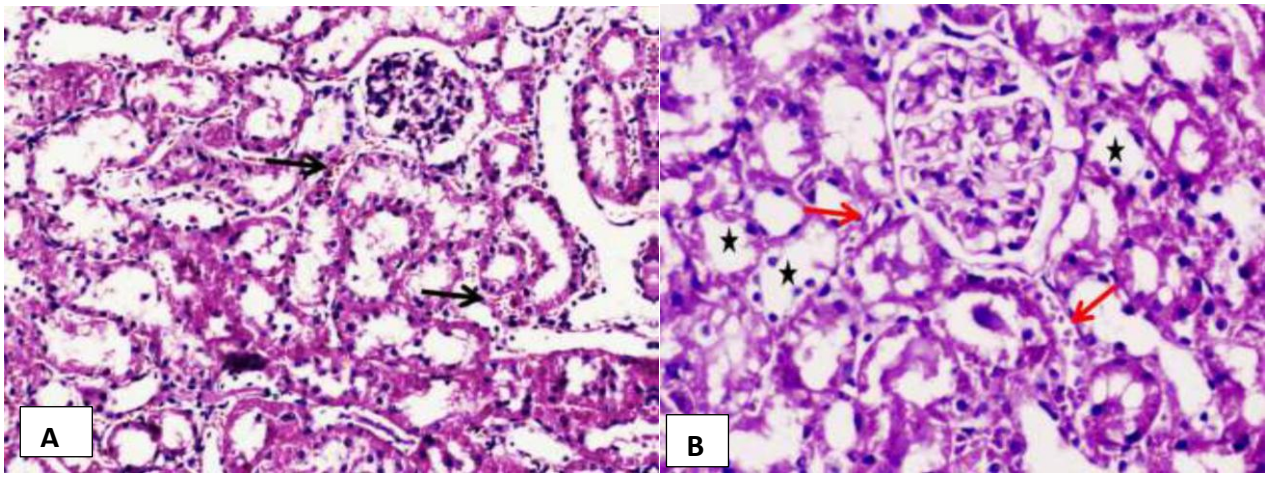

Fig. 3. Histopathology changes in the right kidney of all rats in cisplatin pretreated group by saxagliptin at the end of experiment

A: Light microscopy of renal section from diseased group treated by saxagliptin demonstrated decrease congestion of both capillary glomerular tuft & interstitial vessels, also tubular degenerative and interstitial inflammatory changes generally were reduced (H&E stain ×200).

B: Light microscopy of renal section from diseased group treated by saxagliptin demonstrated slightly normal capillary glomerular tuft & mild interstitial congestion, also few tubules showed degenerative hydropic changes with absence of interstitial inflammatory cells (H&E stain ×400).

4-Discussion:

Cisplatin is a chemotherapy that used widely in the treatment of solid tumors. Nephrotoxicity is the most common side effect which limits the clinical use of cisplatin and seriously worsens the quality of life of cancer patients resulting in dose reduction and discontinuation of treatment (18).

Various mechanisms for pathogenesis of cisplatin induced nephrotoxicity were documented including oxidative stress, inflammation, and activation of apoptotic pathways (19;20).

DPP-4 inhibitors are widely used antihyperglycemic agents, which act to promote the pancreatic β-cell function via prevention of the inactivation of GLP1. Recently, the pleiotropic extra pancreatic actions of DPP-4 inhibitors have drawn much attention owing to their potential applications in various diseases (21).

The present study showed a significant decrease in the body weight manifested by decrease of the body weight percentage in the cisplatin-treated group compared to normal control group at the end of the experiment, this result was in agreement with Wang et al.,2019 (22) who reported that there was significant weight loss with cisplatin-induced nephrotoxicity in rats that received 5mg/kg cisplatin for 21 days. The weight loss observed was due to gastrointestinal toxicity, reduced ingestion of food, increased catabolism, physiological and psycological imbalance (23). In saxagliptin pretreated group there were significant decrease in the body weights of rats as manifested by decrease in percentage of change in the body weights in the saxagliptin treated group, these were in agreement with Abdel-Aal et al., 2020 (24) who reported that Stevia aqueous extract, saxagliptin and their combination showed a significant decrease in body weight due to reduction of food and water intake .Also, it was reported that saxagliptin reduced water intake in diabetic mice (25).

Concerning kidneys weight, the present study showed that the absolute kidney weight was significantly increased in the cisplatin-treated group compared to the normal control group which was in agreement with Wang et al., 2019 (22) who reported that there was an increase in the kidney weight observed in groups treated with cisplatin and correlated with edema or inflammation due to cisplatin-induced tubular necrosis (26). Previous reports documented that in animals treated with CP, the kidneys weight increased, and this was correlated with the intensity of tissue damage (27;28). , saxagliptin pretreatment alleviated this increase in absolute kidney weight in rats and there was a significant decrease in absolute kidney weight which might be due

to its anti-inflammatory in accordance with Helal et al., 2018 (29).

Results of the present study showed significant decrease in GSH, catalase level in the cisplatin treated group compared to the normal control group, while a significant increase in the MDA level in the cisplatin treated group compared to the normal control group. These results were in line with Abdel Moneim et al., (30), and Ali et al., (31).

Three mechanisms have been proposed to account for ROS generation. First, cisplatin is aquated into a highly reactive form, which can rapidly react with thiol-containing proteins including glutathione. Cisplatin with depletion or inactivation of glutathione and related antioxidants leads the accumulation of endogenous ROS and oxidative stress in the cells. Second, cisplatin may induce the mitochondrial dysfunction and increase the ROS production via disruption of the respiratory chain. Finally, cisplatin may induce the ROS formation in the microsomes via the cytochrome P450 system (32). Saxagliptin pretreatment alleviated these changes, the levels of GSH, catalase were significantly increased while, there was significant decrease in MDA level, these results were due to anti-oxidant effects of saxagliptin. This was in accordance with Helal et al., 2018(29), and Abdelrahman et al., 2019 (33).

The present study showed that cisplatin induced significant increase in the level of TNF-α in kidney tissue, this was in agreement with the previous investigation of Kumar et al., 2017 (34), and Zhu et al., 2017 (35).

Subsequent studies had shown that TNF-α plays a critical role in the induction of proinflammatory mediators and recruitment of inflammatory cells during cisplatin-induced nephrotoxicity in mice and it appears to play a central role in the activation of this cytokine response and also in the pathogenesis of cisplatin renal injury (36) .

The level of TNF-α was declined in cisplatin group pretreated by saxagliptin, this was in the line with Choi et al., 2017(37).

It was demonstrated that saxagliptin pretreatment could alleviate drug induced toxicity via reducing oxidative damage and its subsequent inflammation and apoptosis. Moreover, animal studies showed that DPP-4 inhibitors significantly reduced glomerulosclerosis, which was also associated with lower plasma TNF-α levels (29) and malondialdehyde immune reactivity, suggesting the anti-inflammatory and antioxidant roles (38).

Moreover, the results of the present study revealed that there was a significant increase in the level of DPP4 in rat's kidneys that received cisplatin and pretreatment with saxagliptin significantly decreased DPP4 level. DPP4 was bound on the surface of

different cellular types, in particular proximal tubular, and endothelial cells (39), it was reported that up-regulation of the glomerular expression of DPP4 had been shown in inflammatory states (40). Also, it was reported that DPP-4 expression was not observed in healthy individuals whereas increased DPP-4 expression was seen in various disease states, including cancer, inflammation, obesity, and diabetes (41).

In the current work, IP injection of cisplatin into rats resulted in the development of destructive renal injury that was associated with significant increase in the levels of serum creatinine and BUN, as well as proteinuria. It was explained by the extensive renal damage that lead to failure of creatinine clearance resulting in the accumulation of creatinine in the blood (42).

Results of the present study were in agreement with the previous study of El Amir et al., 2019 (43), and Abdel-Razek et al., 2020 (44).Also, cisplatin in the current study significantly decreased the urine volume and this result was in contrast with Ali et al., 2020 (45) .The decrease in urine volume in the present study may be related to the oliguric phase of acute kidney injury.

The current study also revealed that cisplatin increased the albuminuria and albumin creatinine ratio which was in line with Abdelrahman et al., 2019 (33). Albuminuria was due to defect in the kidney ability to concentrate the urine leading to increased excretion of proteins (46). Pretreatment with saxagliptin alleviated all these changes and there was significant increase in urine volume with significant amelioration of increased serum creatinine, BUN and albuminuria. These results were in agreement with Helal et al., 2018 (29), and Al Suleimani et al., 2018 (47).

Saxagliptin inhibited renal DPP-4 activity more potently than other DPP4inhibitor sitagliptin, and the inhibitory action of saxagliptin was associated with improvements in albuminuria (48). Covalent binding of saxagliptin and DPP-4 may contribute to potent membrane-bound DPP-4 inhibition in glomerular and tubular cells (49).

Histopathological findings of the present study also supported the biochemical results in cisplatin group and showed the clear signs of severe nephrotoxicity in the form of massive glomerular and tubular degenerative changes ,necrosis, tubulointerstitial nephritis and dilation of the tubular lumen with intraluminal blood extravasation, vacuolation (fat deposit), and epithelial desquamation, infiltration of inflammatory cells, congestion, glomerulus atrophy, inflammation between the tubules and tissue necrosis of the renal cells in the kidney of experimental rats which in contrast to the normal control rats , these results were in accordance with previous reports of Shalaby et al.,2014(50), and

Prabhu et al., 2013(51). saxagliptin pretreatment showed general improvement of the histopathological picture regarding inflammatory cell infiltration and necrosis of renal tubules. This was in accordance with Helal et al., 2018 (29).

5-Conclusion, Recommendations:

This study concluded that saxagliptin with its potential antioxidant and anti-inflammatory effects can prevent and protect the kidney tissue from damage caused by cisplatin via long lasting inhibition of DPP4 enzyme and its tight covalent binding. Further studies are needed with different doses and may be for longer duration, on a larger sample size to fully investigate the effect of saxagliptin on cisplatin induced nephrotoxicity. Also, more studies targeting the side effects of saxagliptin should be addressed.

6-References:

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