Protective effects of sitagliptin on cholemic nephropathy: the role of sesterin2, and Nrf2/SOD pathway

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Research Article

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Abstract

Background

Cholestasis or bile duct ligation (BDL) could develop cirrhosis and may lead to other organ dysfunction, including kidneys which, is called cholemic nephropathy (CN). Hyperbilirubinemia, bile acid accumulation, renal hypoperfusion, oxidative stress, and inflammation are implicated in the pathogenesis of CN. Sitagliptin is an oral antihyperglycemic drug with anti-inflammatory and anti-oxidative effects. The effects of sitagliptin on CN is unknown.

Methods

BDL was performed to induce CN model in 42 male Wistar rats (200–250 gr), which were divided equally into six groups: sham-operated received distilled water as the vehicle (sham + veh), sham received 50mg/kg sitagliptin (sham + sit 50), BDL group, BDL + sit 10, BDL + sit 50, BDL + sit 100 groups, received sitagliptin 10, 50, and 100mg/Kg respectively for 14 days by gavage. Aspartate transferase, alkaline phosphatase, total bilirubin (T-Bil), serum and urine biomarkers of renal function, redox system status, TNF-α, and renal histopathology were assessed.

Results

Induction of BDL increased serum liver enzymes, T-Bil, creatinine (Cr), urea, urine Cr, albumin to Cr ratio, and decreased Cr clearance. Renal sestrin2, malondialdehyde, TNF-α, renal index, and kidney tissue injury score were elevated, while superoxide dismutase activity, total antioxidant capacity, and nuclear factor erythroid 2–related factor 2 (Nrf2) were reduced. Treatment with sitagliptin especially in low dose reverse these effects.

Conclusions

Sitagliptin improves renal injury and function via ameliorating inflammation and oxidative stress by activating Nrf2/SOD pathway in BDL rats. Sitagliptin might be helpful in treating renal complications in cirrhosis and severe liver disease.

1. Background

Severe hepatic disorders due to alcoholic or non-alcoholic liver disease may lead to other organ dysfunction including, kidneys among vital organs, which is known as hepatorenal syndrome (HRS) [1]. Cholestasis or bile duct ligation (BDL) caused liver impairment is a clinical complication that could develop cirrhosis, fibrosis, and liver failure [2]. Mechanistically, renal injury as a consequence of cirrhosis is due to circulatory and hemodynamic alterations. Splanchnic arterial vasodilation, reduced total

peripheral resistance, blood volume depletion, and hypotension, activates several mechanisms to maintain blood pressure including, the sympathetic nervous system, renin-angiotensin system and hormone secretion [1]. Accumulation of bile acids and bilirubin in cholestasis could play a cytotoxic role for renal cells[3]. Several evidences support from influences of oxidative stress and inflammation in hepatic and renal damage in cholestasis [4]. Increase in production of reactive oxygen species, lipid peroxidation, and protein carbonylation, as well as elevation of pro-inflammatory cytokines in liver and renal tissue of cholestatic rats are reported [5]. Acute kidney injury occurs in 20–50% of cirrhotic hospitalized patients [6]. Accompanied by the progression of liver disease, renal vasoconstriction is reported, which could damage renal function, in late stages reduce glomerular filtration rate (GFR), and increase serum creatinine [7]. Cholestasis increases HRS susceptibility through the elevation of portal vein pressure and cirrhosis [8], so it is an acceptable experimental model to assess the pathophysiology of cirrhosis and HRS.

Sitagliptin is a dipeptidyl peptidase-4 (DPP4) enzyme inhibitor, which is prescribed to treat type 2 diabetes mellitus [9]. In the literature, there are several documents that reported the renoprotective effects of DPP4 inhibitors and sitagliptin in diabetic animals through the elimination of oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress [10]. Hence, this study is designed to determine whether sitagliptin could ameliorate CN in experimental cholestatic rats, and also to assess the antioxidant and anti-inflammatory action of sitagliptin as possible mechanisms.

2. Methods

2.1 Animals

In this study, 42 male Wistar rats (200–250 gr) were purchased from the animal house of Kerman University of Medical Sciences (Kerman, Iran). They were housed in cages with free access to food and water under 24 ± 2°C temperature and a 12 hr light/dark cycle (Fig. 1B). The Ethics Committee of Kerman University of Medical Sciences, Iran was, approved the protocol of the experiment (IR.KMU.AH.REC.1401.264(.

2.2 Experimental groups and surgical procedures

The animals were divided into six groups (n = 7): Sham, Sham + sitagliptin 50 mg/kg, bile duct ligation (BDL + Veh), BDL + sitagliptin 10 mg/kg, BDL + sitagliptin 50 mg/kg, BDL + sitagliptin 100 mg/kg (Fig. 1A). To perform the bile duct ligation (BDL), rats were anesthetized with injections of ketamine (100 mg/kg) and xylazine (10 mg/kg) cocktail intraperitoneally (IP). The abdomen was opened with a mid-line incision (approximately 2 cm). After the observation of the bile duct, it was ligated by two surgical knots with surgery silk 5 – 0 at the proximal and distal. After BDL, 1 ml of 0.9% sodium chloride solution was injected into the peritoneal cavity to maintain the physiological condition. Then the two layers of the abdomen (muscle and skin) were sutured separately with 4 – 0 silk thread [9]. In the Sham groups, the laparotomy was performed without ligation of the bile duct. Doses of 10, 50, and 100 mg/kg of sitagliptin

(donated by Jalinous Pharmaceutical Co. Iran) were given to the treatment groups orally (PO) for two weeks. The animals in the sham groups were given the distilled water during the same period and volume. On the day 14, animals were placed in metabolic cages to collect the 24-hour urine samples. On day 15, after measuring the body weight with a digital scale, animals were anesthetized by ketamine/xylazine (100/10 mg/ kg, IP), blood samples were collected from the heart, centrifuged, and the serum were frozen at − 80°C for the assessment of serum parameters. Finally, the kidney tissues of the animals were taken out of the body, after weighing, the right kidneys were placed in 10% buffered formalin (pH 7.4) for pathological examination, and the left kidneys were stored at -80°C for to examine tissue parameters. The kidney weight index was calculated by the following formula:

$$\mathrm{kidneyweightindex} = \frac{\mathrm{kidneyweight\,(mg)}}{\mathrm{bodyweight\,(gr)}}$$

2.3 Histopathological examinations

Left kidney tissues were fixed with 4% buffered paraformaldehyde were embedded in paraffin, and 2-µm-thick sections were prepared. Hematoxylin and eosin (H&E) staining was used to evaluate tissue damage and inflammation. The sections were examined with an Olympus microscope (CX41, Tokyo, Japan) by an expert pathologist who were blind to the groups. For quantitative damage scoring, six fields in each sample were selected and scored from 0–5 (magnification x 100 or 400). The scores described as: 0 = normal, 1 = damage up to 10%, 2 = damage 10–25%, 3 = damage 25–50%, and 4 = damage 50–75%%, 5 = damage more than 75% [11].

2.4 Assessment of serum and urine Urea, creatinine, and albumin

The urine and serum levels of urea, creatinine, and albumin were measured by Commercial kits (Pars Azmoon, Tehran, Iran) using an autoanalyzer (Selectra-XL, Vital Science, Netherlands). The urine albumin to creatinine ratio (ACR) was calculated according to the following formula:

$$\mathrm{Urinealbumintocreatinineratio\,(ACR)} = \frac{\mathrm{Urinealbumin(mg/dl)}}{\mathrm{Urinecreatinine(mg/dl)}}$$

In order to measure the renal clearance of creatinine to estimate GFR, urinary creatinine concentration (Ucr), plasma creatinine concentration (Pcr), and urine volume (UV) were used, and GFR was calculated according to the following formula [12]:

$$\mathrm{Glomerularfiltrationrate} = \frac{\mathrm{Ucr} \times \mathrm{UV}}{\mathrm{Pcr}}$$

2.5 Liver enzymes assay

The activity of liver enzymes (ALT, AST) and T-BIL in serum was measured using the standard kit (Pars Azmoon, Tehran, Iran) by enzymatic method.

2.6 The Determination of renal oxidant/antioxidant activity

To measure the level of malondialdehyde, superoxide dismutase, and total antioxidant capacity, the kidney tissues were homogenized in 1.5% KCL solution and then centrifuged for 10 minutes at 1000 rpm. The thiobarbituric acid method was used for MDA assessment. Briefly, the homogenized tissues of the kidney were mixed with trichloroacetic acid and thiobarbituric acid (TBA), then placed in a boiling water bath for 45 minutes, after cooling and adding n-butanol, the absorbance were measured at 534 nm [13]. The TAC was measured by the ferric reducing/antioxidant power (FRAP) method. Briefly, 5 µL of plasma and 70 µL of FRAP reagent were mixed. Distilled water was used as a blank, the mixture was incubated at 37 ℃ for 5 minutes, then the absorbance was red at 593 nm [14]. The superoxide dismutase (SOD) activities in the kidney tissue homogenates were determined according to the Randox kit instructions (UK; Cat NO.RS504). The absorbance of SOD was measured at 570nm.

2.7 ELISA assay

Renal levels of Nrf2, sestn2, and TNF-α were measured using commercial ELISA kits (R&D, USA).

2.8 Statistical Analysis

GraphPad Prism version 8 was used for statistical analysis. The data normality was checked with the Shapiro-Wilk test. One-way ANOVA statistical analysis with Tukey's post hoc test was used for normally distributed data with more than two groups. The Kruskal-Wallis's test followed by the Mann-Whitney U test was used for non-normally distributed data. The data were expressed as means ± SEM. $P < 0.05$ was considered statistically significant.

3. Results

3.1 The effects of sitagliptin on the body, and kidney weight

Induction of two weeks of BDL in animals decreased percentages of body weight change. Sitagliptin treatment at the dose of 10mg/kg returns this decrease. Kidney weight index increased in ligated groups ($P < 0.05$). A slight insignificant reduction of this index was seen in the BDL + Sit10 group (Fig. 2A, B).

3.2 The effects of sitagliptin on serum biomarkers

3.2.1 Serum liver enzymes

Serum AST level was increased in the BDL + VEH group ($P < 0.001$). Sitagliptin at the dose of 10mg/kg reduced it to almost sham level, while doses of 50 and 100mg/kg could not reduce this enzyme level significantly (Fig. 2C)

Serum ALT also was increased in the ligated group ($P < 0.001$). Like AST, only the low dose of sitagliptin reduced ALT level, while the other two doses caused more elevation in comparison to the sham group ($P < 0.001$) (Fig. 2D).

3.2.2 Serum total bilirubin levels

In consequence of two weeks of BDL, serum T-bil level were increased ($P < 0.001$). None of sitagliptin doses could reduce this marker (Fig. 2E).

3.2.3 Serum creatinine, urea, and albumin

Scr and Surea were increased in the BDL + Veh group ($P < 0.01$, $P < 0.0001$). Although, Surea was reduced by all doses of sitagliptin, Scr reduction was seen just in the BDL + Sit10 group. Neither induction of BDL, nor sitagliptin treatment affected serum albumin levels (Fig. 3A-C).

3.3 The effects of sitagliptin on urine biomarkers

3.3.1 Urine creatinine, and albumin/creatinine ratio

Ucr level was reduced in the ligated group ($P < 0.01$). Sitagliptin treatment at the dose of 100mg/kg increased this parameter. UACR was increased in the BDL + Veh group ($p < 0.01$), and sitagliptin reversed this ratio dose-dependently (Fig. 3D, E).

3.3.2 Glomerular filtration rate

Induction of BDL eliminated GFR, and 10 mg/kg sitagliptin administration improved renal filtration compared to the BDL + Veh group ($P < 0.01$) (Fig. 3-F).

3.4 The effects of sitagliptin on the renal activity of redox system, Nrf2, and sestrin2 levels

Alleviation of TAC, TAC/MDA ratio, SOD, and Nrf2 were seen in the kidney of cholestatic animals. Also, lipid peroxidation and sestrin2 level were increased in this tissue. Sitagliptin improved these parameters in all doses, although the MDA level was affected only by 10 mg/kg sitagliptin administration (Fig. 4A-F).

3.5 The effect of sitagliptin on renal TNF-α

The TNF-α level was elevated in the kidney tissue of ligated animals ($P < 0.0001$). Sitagliptin at all doses reduced this inflammatory cytokine (Fig. 4G).

3.6 The effect of sitagliptin on renal histopathology

The histopathologic alterations, including tubular cell swelling, brush border loss, protein cast, deposition of bile pigments, interstitial inflammation, vascular congestion, and edema, were observed in H&E-

staining assessment of kidney tissue in cholestatic rats. Kidney tubular injury score (KTIS) was reduced in the BDL + Sit10 group ($P < 0.01$) (Fig. 5).

4. Discussion

Cholestasis-induced nephropathy also called cholemic nephropathy is a prevalent disorder in cholestasis patients. The primary role of oxidative stress in the pathogenesis of CN is mentioned in previous studies [15]. Thus, in our present study, we used BDL-induced nephropathic rats to investigate the potential mechanism of sitagliptin on renal injury and oxidative stress of CN.

Hyperbilirubinemia in cholestasis develops renal injury and structural disturbance. Bile acids inhibit electrolyte transporters in the renal tubules in a way that increases tubular acidity which favors cast formation and leads to tubular obstruction [16]. Another mechanism of CN is due to renal hemodynamic alteration. High serum bilirubin exerts a negative effect on cardiac contractility and rhythmicity that contributes to poor renal perfusion [17]. In addition, bile acid accumulation is cytotoxic, impaired mitochondrial function, and elevated reactive oxygen specious (ROS) formation [18]. Direct nephrotoxicity of bilirubin and bile salts is proved. The presence of 66% acute kidney injury was reported in renal biopsy of bile cast-positive patients who suffered from severe liver disease [2].

In the current study, deposition of bile pigments, tubular injury, and interstitial inflammation were seen in the kidney tissue. Also, we observed enhancement of oxidative stress biomarkers, lipid peroxidation, and inflammatory cytokine TNF-α in the kidneys of cholestatic groups. Our findings were in line with investigations that mentioned the involvement of oxidative stress in the pathogenesis of CN (4).

DPP-4 inhibitors like sitagliptin, an oral anti-hyperglycemic drug, reveal renoprotective effects in diabetic and non-diabetic conditions as anti-oxidant agents [10]. In an experimental model of xenobiotic-induced nephrotoxicity, sitagliptin ameliorated renal injury by augmentation of anti-oxidant defense and Nrf2/HO-1 pathway up-regulation [19]. The Kelch-like ECH-associated protein 1 (Keap1)–Nrf2-antioxidant response element system is the main pathway activated in oxidative stress states. The ablation or disrupted activation of Nrf2 accelerates oxidative stress conditions and disrupts normal cellular redox balance, leading to cell dysfunction [20]. In severe acute pancreatitis-related acute lung injury, sitagliptin could mitigate oxidative stress by activating Keap1–Nrf2 signaling pathway [21]. Nrf2 is a transcription factor, up-regulates downstream antioxidant enzymes, SOD and catalase, in stress states [22]. Nrf2-deficiency in mice aggravates oxidative stress, inflammation, and renal injury in diabetic models [23]. Moreover, increased Nrf2 activity preserves mitochondrial function and morphology [24]. The latter observations support renal protection mediated by Nrf2 through antioxidant and anti-inflammatory functions. In agreement with other research, our data reveals an increment of Nrf2 level, SOD activity, TAC, and TAC/MDA ratio accompanied by reduction of TNF-α and histopathologic alterations in renal tissue of cholestatic rats by sitagliptin treatment. On the other hand, the beneficial effect of sitagliptin administration on cardiac performance and histology is reported in a 5/6 nephrectomized model of

chronic kidney disease [25]. This cardio-protective action of sitagliptin could help restore renal circulation and improvement of renal function and histology in CN.

Sestrin2, a member of a family of highly conserved antioxidant proteins, regulates intracellular ROS levels in hypoxia, oxidative stress, and DNA damage [26]. Yang et al. explained the contribution of renal sesn2 in the maintenance of redox balance [26]. Overexpression of sesn2 in BDL mouse liver and bile acid-treated HepG2 cells reveals the hepatoprotective effect of sesn2 against bile acid-induced endoplasmic reticulum stress [27]. Our results confirmed the involvement of sesn2 in oxidative stress induced by cholestasis in renal tissue. Sitagliptin might improve renal damage via accretion of sesn2 level in BDL rats.

Conclusions

Collectively, our findings revealed the renoprotective effects of sitagliptin in cholestasis via reducing inflammation, oxidative stress, and sesn2 through the Nrf2/SOD pathway. As sitagliptin is an FDA-approved drug that is used to treat diabetic patients, we suggest considering it to alleviate renal injury and dysfunction in cirrhosis and severe liver disease.

Abbreviations

HRS
hepatorenal syndrome
BDL
bile duct ligation
CN
cholemic nephropathy
Sit
Sitagliptin
TNF-α
Tumor necrosis factor alpha
T-Bil
Total bilirubin
Cr
creatinine
Sesn2
Sestrin2
MDA
Malondialdehyde
SOD
Superoxide dismutase
TAC
Total anti-oxidant capacity

Nrf2
Nuclear Factor Erythroid 2-Related Factor 2
ROS
Reactive Oxygen Species
GFR
Glomerular filtration rate
DDP4
Dipeptidyl peptidase-4
IP
Intraperitoneally
H&E
Hematoxylin and eosin
UACR
Urine albumin to creatinine ratio
Ucr
Urinary creatinine concentration
Pcr
Plasma creatinine concentration
UV
urine volume
AST
Aspartate transferase
ALT
Alkaline transferase
TBA
Thiobarbituric acid
FRAP
Ferric reducing/antioxidant power
Surea
Serum urea
HO-1
Heme oxygenase-1
Keap1
Kelch-like ECH-associated protein 1
ARE
Antioxidant response element Availability of data and materials

Declarations

Not applicable.

Ethics approval and consent to participate

The Ethics Committee of Kerman University of Medical Sciences, Iran was approved the protocol of experiment (IR.KMU.AH.REC.1401.264).

Consent for publication

Not applicable.

Competing interests

All the authors are in favor of publishing the manuscript in this journal. The authors declare that they have no competing interests.

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Author contributions

MA participated in the experimental procedures, statistical analysis and drafting, MK participated in the design and coordination of the study, MA participated in drafting, EJ participated in pathology scoring, and SS participated in the design and coordination of the study, drafting of the manuscript, statistical analysis, interpreting the findings, and final revise of manuscript. All authors read and approved the final manuscript.

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Figures

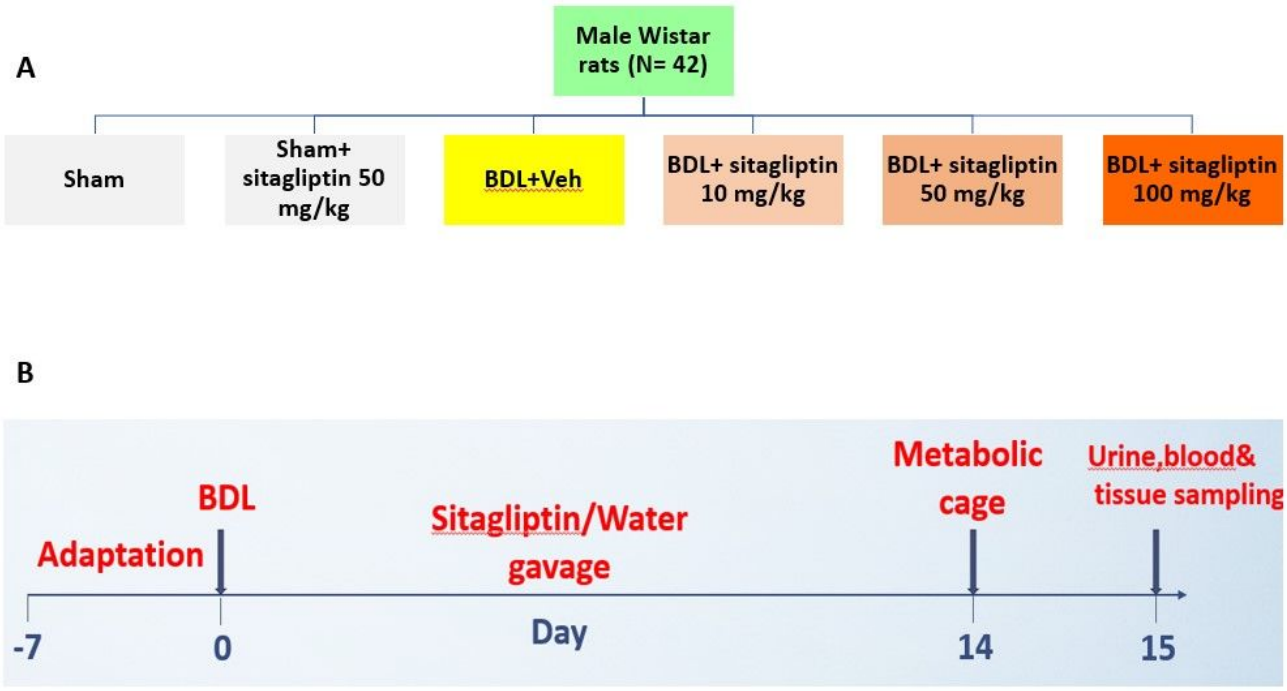

Figure 1

Schematic representation of the experimental groups (A), and timeline of the study (B). Sit: sitagliptin, BDL: bile duct ligation, Veh: vehicle.

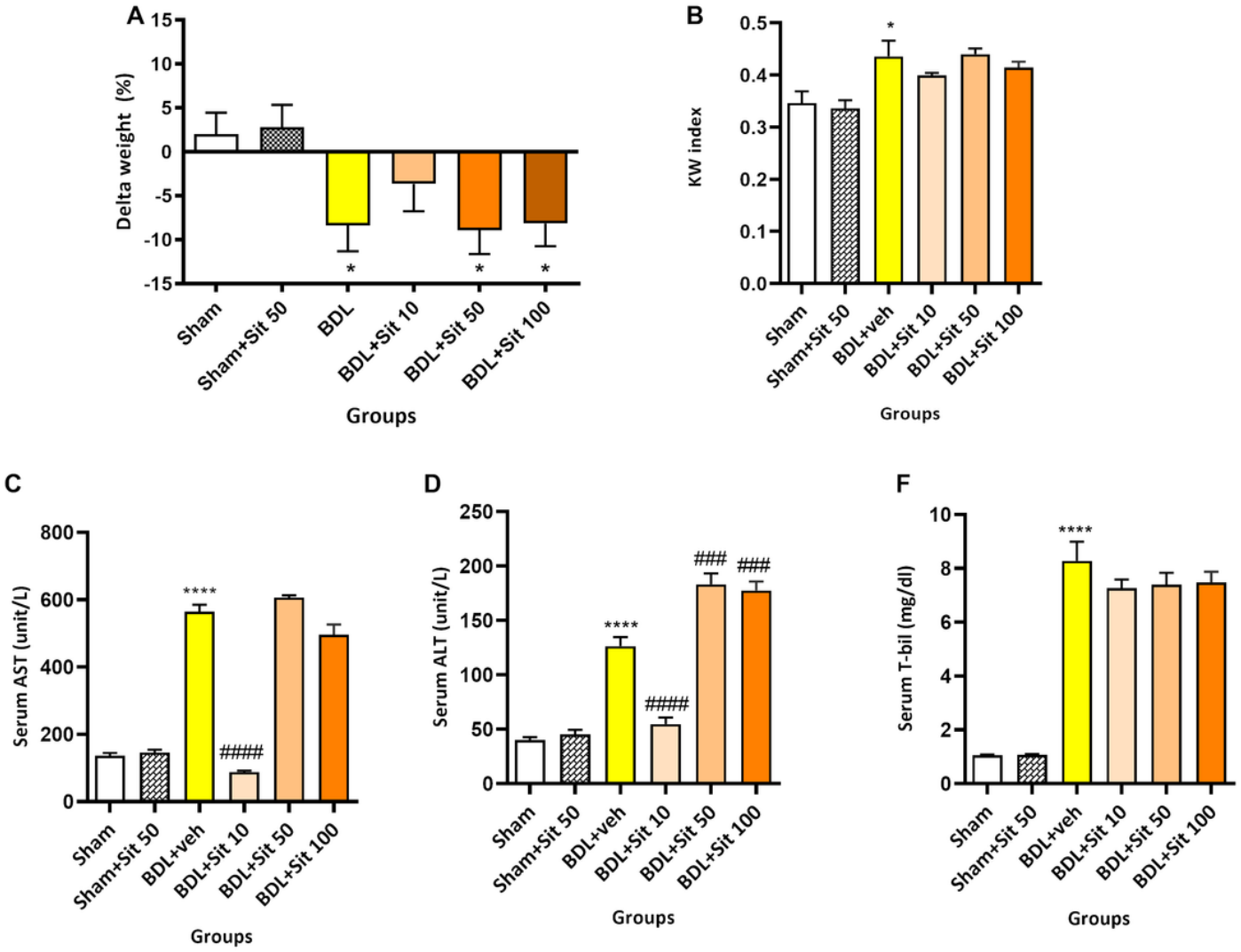

Figure 2

Effect of sitagliptin on the percentage of body weight (BW), Kidney weight (KW) index, serum levels of aspartate aminotransferase (AST), alkaline transferase (ALT), and total bilirubin (T-bil). *P<0.05, ****P<0.0001 *VS* Sham, ### P<0.001, #### P<0.0001 *VS* BDL+Veh, ++++ P<0.0001 *VS* BDL+Sit10, ^^ P<0.01 *VS* BDL+Sit50; (mean±SEM, n=7).

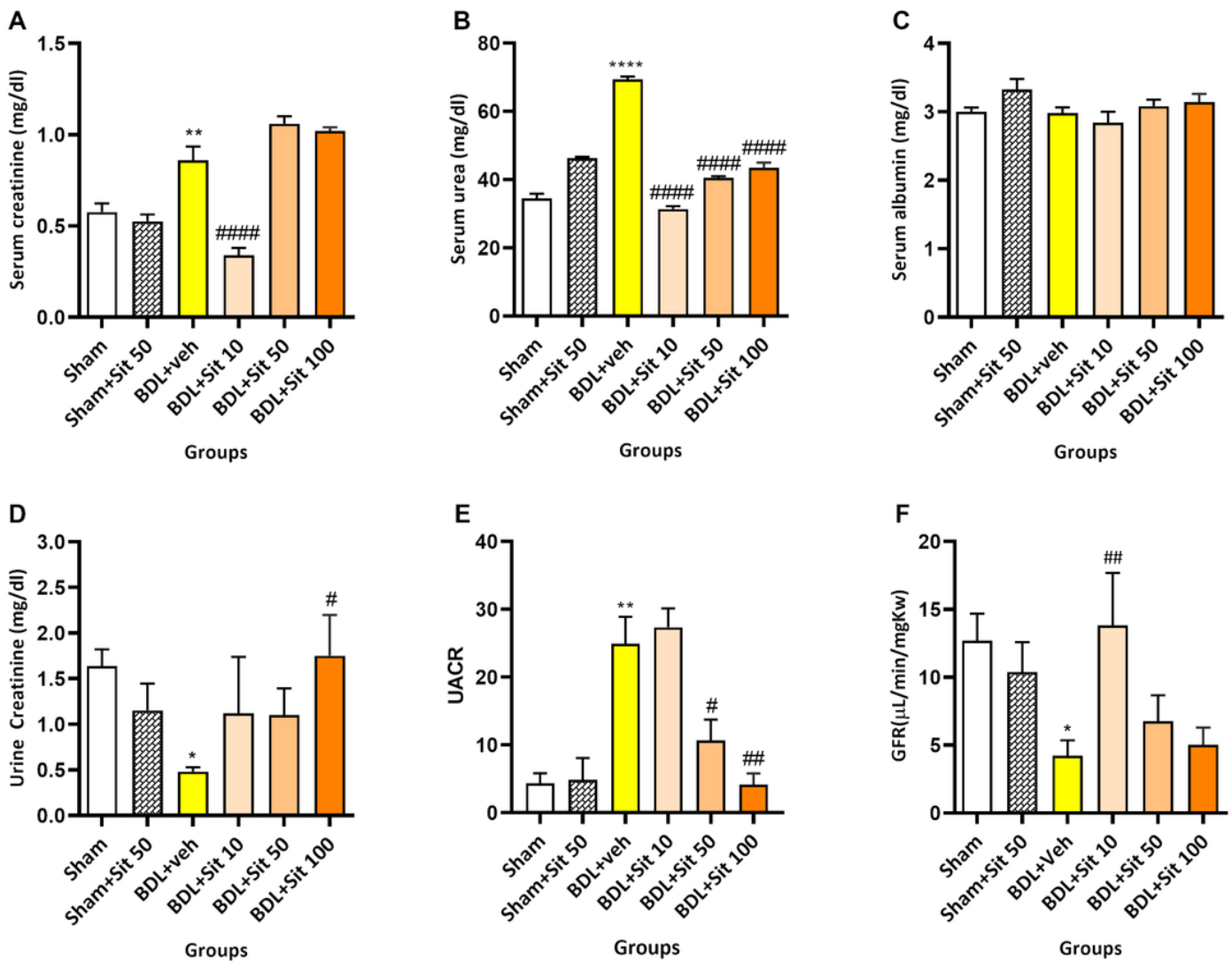

Figure 3

Effect of sitagliptin on serum levels of creatinine, urea, albumin, urine level of Cr (UCr), urine albumin to UCr ratio (UACR), and glomerular filtration rate (GFR); *P<0.05, **P<0.01, ****P<0.0001 *VS* Sham, # P<0.05, ## P<0.01, #### P<0.0001 *VS* BDL+Veh, +P<0.05, ++ P<0.01, ++++ P<0.0001 *VS* BDL+Sit10; (mean±SEM, n=7).

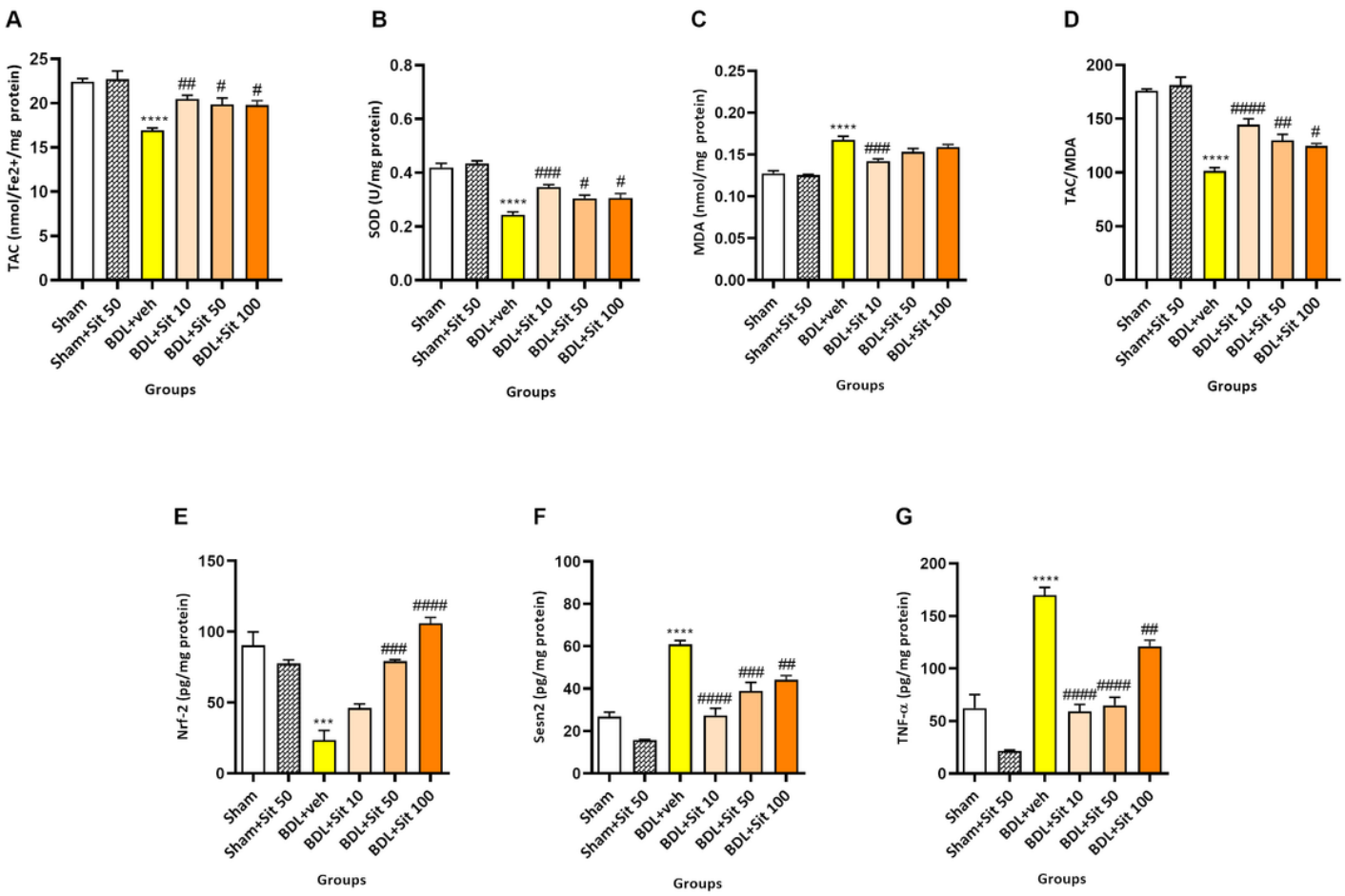

Figure 4

Effect of sitagliptin on kidney level of total anti-oxidant capacity (TAC), TAC to malondialdehyde ratio (TAC/MDA), superoxide dismutase (SOD) activity, Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2), MDA, sestrin2 (sesn2), and Tumor necrosis factor alpha (TNF-α) levels. ***P<0.001, ****P<0.0001 *VS* Sham, # P<0.05,## P<0.01, ### P<0.001, #### P<0.0001 *VS* BDL+Veh, +P<0.05, ++ P<0.01 *VS* BDL+Sit10, ^^ P<0.01 *VS* BDL+Sit50; (mean±SEM, n=7).

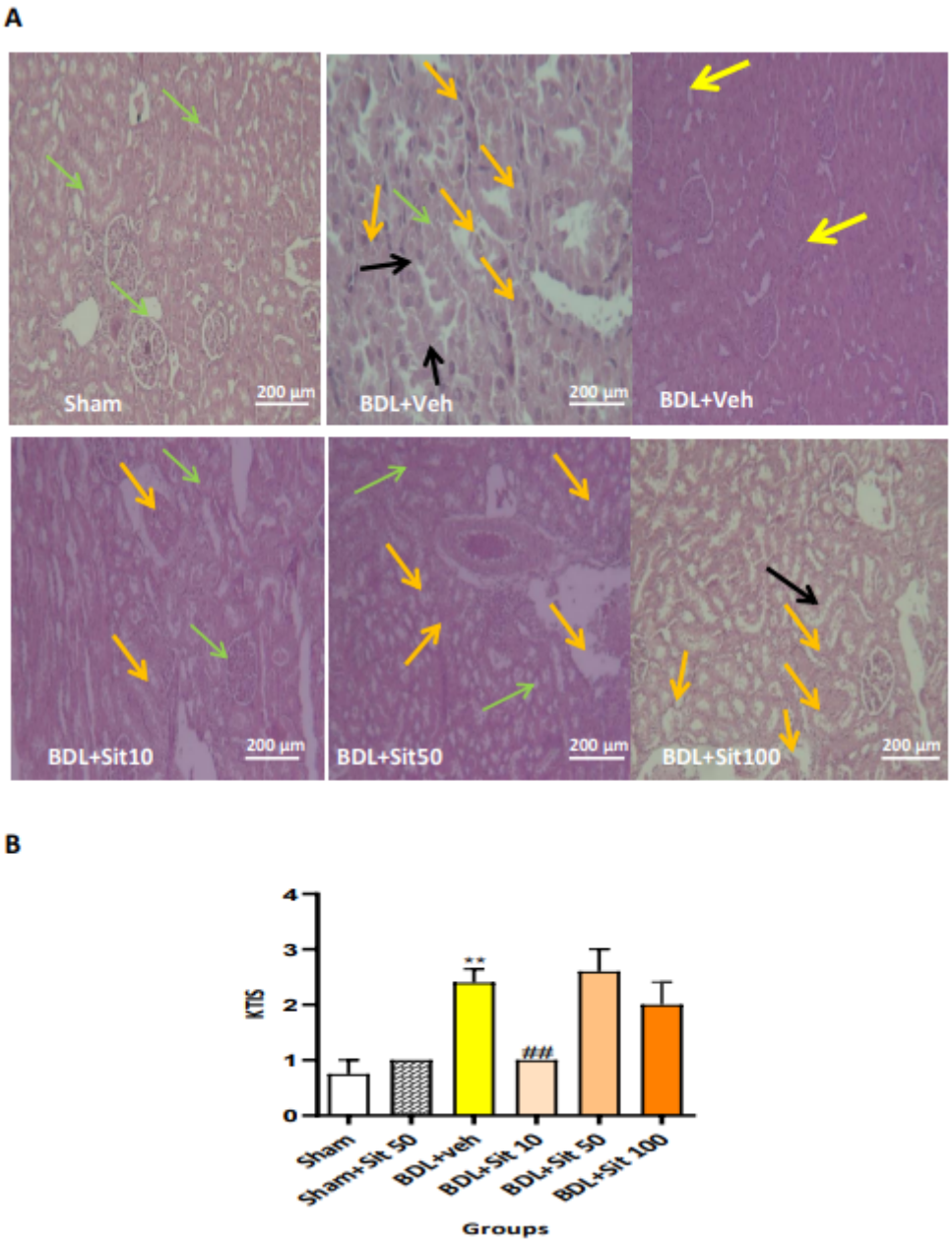

Figure 5

Representative H&E staining of kidney sections from studied groups (magnification ×100), and Quantitative analysis of the kidney tubular injury score (KTIS). **P<0.01 *VS* Sham, ## P<0.01 *VS* BDL+Veh; (mean ± SEM, n=5)

Supplementary Files

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