



THE POTENTIAL MODULATING IMPACT OF THE DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITOR, SITAGLIPTIN ON STREPTOZOTOCIN-NICOTINAMIDE-INDUCED DIABETIC NEPHROPATHY IN RATS

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The main risk factor for the onset and development of diabetic nephropathy (DN) is hyperglycemia. Kidney end-stage disease is brought on by DN, a significant microvascular consequence of diabetes. In this study, we evaluated the renoprotective potential of sitagliptin in a rat model of streptozotocin-nicotinamide-induced DN. Following the intraperitoneal treatment of rats with 110 mg/kg nicotinamide followed 15 min by 60 mg/kg streptozotocin, DN manifested in rats after 8 weeks. Fasting blood glucose, postprandial blood glucose, HbA1c, serum urea and creatinine, and urine albumin levels were assessed in control, DN, and DN rats treated with sitagliptin. Additionally, paraffin-embedded kidney segment histopathological assessment was carried out. The increased levels of fasting, postprandial blood glucose, and HbA1c were decreased with sitagliptin. Sitagliptin restored the changes in kidney structure and function brought on by DN. The findings suggest that sitagliptin could prevent DN by stringent glycemic management, restoring the kidneys' declining function and protecting their structure.

Keywords: Streptozotocin; Diabetic nephropathy; Sitagliptin; Kidney function and structure.

INTRODUCTION

With a swiftly rising incidence, diabetes mellitus (DM) is the fifth most common cause of death in emerging nations¹. The most prevalent form of diabetes in adults is type² diabetes mellitus (T2DM), which makes up 90–95 percent of cases. It is a condition brought on by a number of variables, including genetics linked to insulin secretion and resistance, environmental influences including ageing, stress, and inactivity, as well as obesity³. It has been demonstrated that incretin insufficiency is crucial to the development of T2DM⁴.

Coronary artery disease, peripheral artery disease, and cerebral artery disease are examples of macrovascular consequences from diabetes (nephropathy, retinopathy, and neuropathy). The primary causes of disease-related morbidity and mortality are these consequences^{5& 6}.

In around one-third of diabetic individuals, diabetic nephropathy (DN) manifests after latency periods of many years⁷. According to recent reports, T2DM⁸ is the most common type of diabetes in those who get DN. As long as the clinical strategy for preventing it does not immediately improve, the growing prevalence of DM and DN are consequently linked⁹. Therefore, in these patients, strict glycemic management and a drop in glycated haemoglobin (HbA1c) level may result in a considerable reduction in microvascular complications¹⁰.

Diabetic kidney disease (DKD), often called DN, is clinically distinguished by a persistent decline in kidney function and a progressive rise in urine albumin levels (microalbuminuria)¹¹. DN and atherosclerosis, two consequences of diabetes, are thought to be significantly mediated by albuminuria¹². Within a decade, 20% of individuals experience DN brought on by microalbuminuria, and 20% of

these patients progress to end-stage kidney disease (ESKD)¹³.

The elevated serum levels of urea and creatinine are two of the most blatant and sensitive signs of renal damage^{14&15}. High levels of blood glucose, and serum urea and creatinine are constant features of DN¹⁶.

The two main incretin hormones released in reaction to the consumption of different nutrients are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). Due to the dipeptidyl peptidase-4 (DPP-4) enzyme's fast destruction, their half-lives are approximately 1-2 mins¹⁷.

Sitagliptin is a common anti-diabetic drug used to treat type 2 diabetic patients and is a powerful and highly selective DPP-4 inhibitor^{18&19}. The protective benefits of DPP-4 inhibitors against diabetes sequelae, such as diabetic retinopathy, neuropathy, diabetic cardiovascular disease, and kidney disease, have been established²⁰. Sitagliptin showed a dose-dependent reno-protective effect in rats with acute renal ischemia/reperfusion (I/R) injury, according to Kawanami *et al.*²¹. Additionally, it was discovered that DPP-4 inhibitors dramatically slowed the development of DN²². Furthermore, treatment of diabetic patients with sitagliptin decreased the incidence of mild to severe acute renal damage, according to a large cohort research by Chao *et al.*,²³.

The fact that DPP-4 is most abundantly expressed in mammalian kidneys and up-regulated in DN, suggests that sitagliptin's DPP-4 inhibition may be a potential treatment strategy for treating DN²⁴. However, the precise mechanisms behind the putative reno-protective effects of DPP-4 inhibitors on the development of DN in diabetic animal models remain to be not fully understood.

Accordingly, the goal of the current study was to examine sitagliptin's possible reno-protective effects in rat models of DN caused by the combination of streptozotocin (STZ) and nicotinamide (NA). The moderating effect of sitagliptin on the biochemical and histological alterations of DN was also evaluated in this study.

MATERIALS AND METHODS

Chemicals

Streptozotocin, nicotinamide, and sitagliptin were obtained from Sigma-Aldrich Co. (U.S.A). All other chemicals were of analytical grade.

Animals

Forty-eight male adult Wistar rats weighing 180-220 g, purchased from animal house of Faculty of Medicine, Assiut University were used in all experiments. The animals were housed in stainless steel cages under a 12 hrs light/dark cycle at 25 °C. Rats were freely allowed to water and food (laboratory chow) *ad libitum*.

Ethical approval

The study was carried out in accordance with the internationally accepted principles for care and use of laboratory animals. The experiments reported here were approved by our institutional ethics committee, with approval number 17200153/2017.

Induction of type 2 diabetes mellitus.

Type 2 diabetes was induced in overnight fasted rats by a single intraperitoneal (i.p.) injection of 110 mg/kg *nicotinamide* (NA) followed after 15 min by a single i.p. injection of 60 mg/kg *streptozotocin* (STZ) freshly prepared in 0.1M cold citrate buffer (pH 4.5)²⁵. After the STZ-NA challenge, the animals were allowed to drink 5% glucose solution for 24 hrs to overcome the initial STZ-induced hypoglycemic mortality.

Blood samples were collected from the tail vein of rats before and after 3 days and 7 days of STZ-NA injection. Blood glucose levels were measured using a hand-held glucometer. Rats with fasting blood glucose levels more than 250 mg/dl on both days were considered as diabetic and used for DN studies^{25&26}. Control animals were treated with equal volumes of saline and citrate buffer.

Experimental design and protocol.

The study was designed in two sets of experiments. In the first set of experiments (preliminary experiments), four groups of rats, 8 rats each were used. Group I and II rats were used as control treated with equal vehicle volumes for 4 and 8 weeks, respectively. Group III rats were the STZ-NA diabetic group that was untreated for 4 weeks, while group IV was STZ-NA diabetic group that was untreated for 8 weeks. At the end of the experimental periods, blood and urine samples were collected from all groups.

In the second set of the experiments (sitagliptin treatment), two groups of rats, 8 rats each. Group I rats were treated with equal

vehicle volumes and used as control, while group II rats were the STZ-NA diabetic group treated with 10 mg/kg/day sitagliptin orally for 7 weeks. At the end of the treatment period, blood and urine samples were collected from both groups.

Assessment of blood glucose and HbA1c levels.

Fasting (overnight fasting) and postprandial (2 hrs after a breakfast) blood glucose levels were determined by obtaining blood samples from the tail vein of rats. Blood glucose levels were measured using a hand-held glucometer. HbA1c levels were quantitatively assayed according to the manufacturer's instructions of rat glycated HbA1c ELISA kit (BioSource, Europe, Belgium).

Collection of 24 h urine.

Urine samples were collected by placing each rat individually in a stainless-steel metabolic cage for 24 hrs, one day before the end of each experimental duration.

Biochemical measurements

At the end of each experimental duration, blood samples were obtained from each rat for biochemical measurements before being sacrificed by decapitation. Blood and urine samples were centrifuged for 10 min. After centrifugation, serum and urine samples were collected, stored at -80°C until assay of urea, creatinine, and albumin. The serum urea level was measured by urease-colorimetric method using a commercially available SPECTRUM Diagnostics Urea/BUN Liquizyme Kit (Egyptian Company for Biotechnology, Cairo, Egypt) according the manufacturer's instructions. The serum level of creatinine was measured by buffered kinetic jaffe reaction without deproteinization method using a commercially available SPECTRUM Creatinine-Jaffe kit (Egyptian Company for Biotechnology, Cairo, Egypt) according the manufacturer's instructions. Albumin urine (microalbuminuria) level was measured by a commercially available BioSystems ALBUMIN (MICROALBUMINURIA) LATEX kit BioSystems S.A., Barcelona, Spain) according the manufacturer's instructions.

Histopathological examination.

Rats were sacrificed, and both kidneys were carefully removed and phosphate-buffered saline cleaned (PBS). The kidneys were cut into longitudinal slices, which were then examined histopathologically. The kidneys were then embedded in paraffin and preserved in neutral buffered formalin at 10%. Hematoxylin and eosin was used to stain micron sections that were cut into 4 to 5 μm thickness (H&E; Tianjin Runtai, Co., Ltd., Tianjin, China). Histopathological observations were made using the HMIAS-2000 Image Analysis System (Guangzhou Longest Technology, Guangzhou, China). The extent of tubular and glomerular damage was then determined from the sections. The degree of glomerulosclerosis, mesangiolysis, and mesangial expansion were used to calculate the Glomerular Damage Index (GDI), which ranged from 0 to 4. From the renal cortex, 80–100 glomerular cells were extracted for each area, observed. By averaging the results from the glomerular cell counts, the GDI was determined²⁷.

In H&E-stained paraffin slices, glomerulosclerosis was semi-quantitatively assessed as follows:

Normal glomerulus is **grade 0**; **Grade 1** features include uneven capillary lumina, starting mesangial growth, and thickening of the basement membrane; **Grade 2**: segmental hyalinosis/sclerosis that affects less than 50% of the glomerular tuft and is mild to moderate; glomerular hyalinosis/sclerosis affecting more than 50% of the tuft, **grade 3** and **Grade 4**: complete tuft obliteration and collapse along with widespread glomerulosclerosis.

Statistical analysis of results.

The results were expressed as the mean \pm standard error of the mean ($X \pm \text{S.E.M}$). Statistical analysis of the difference between groups was done using the one-way analysis of variance (ANOVA) followed by Tukey method test as post hoc analysis. All statistics were carried out using GraphPad Prism software (GraphPad; San Diego CA, USA).

RESULTS AND DISCUSSION

Results of the first set of experiments (preliminary experiments).

Effect of STZ-NA on the fasting blood glucose level.

Treatment of rats with 60 mg/kg STZ i.p. 15 mins after administration of 110 mg/kg NA i.p. produced a significant increase in the fasting blood glucose levels after 3 days ($p < 0.01$, Table 1) and one week ($p < 0.01$, Table 1) as compared to the control rats.

It is evident from the same table that treatment of rats with STZ-NA also produced a persistent significant increase in the blood

glucose levels after 4 ($p < 0.01$) and 8 ($p < 0.01$) weeks as compared to the control rats.

Effect of STZ-NA on post-prandial blood glucose and HbA1c levels.

STZ-NA administration induced a significant increase in the post-prandial blood glucose level when measured 2 hrs after breakfast after 8 weeks ($p < 0.01$, Table 2) in comparison to the control rats.

Furthermore, STZ-NA administration significantly increased the HbA1c level after 8 weeks ($p < 0.01$, Table 2) as compared to the control rats.

Table 1: Effect of intraperitoneal (i.p.) administration of 60 mg/kg streptozotocin (STZ) and 110 mg/kg nicotinamide (NA) to rats on fasting blood glucose level.

Treatment	Time of measurement				
	Before	After 3 days	After 1 week	After 4 weeks	After 8 weeks
Control	113.80 ± 2.37	114.81 ± 2.37	114.92 ± 2.37	116.90 ± 1.67	114.82 ± 2.37
STZ-NA	115.73 ± 3.15	473.3 ± 13.60 **	533.34 ± 19.99 **	532.94 ± 14.99 **	561.67 ± 19.29 **

Blood samples were collected from the tail vein before and after 3 days, 1, 4 and 8 weeks of STZ-NA injection. Each value represents the mean ± S.E.M. of 8 observations, ** Significant difference at $p < 0.01$ vs. control values.

Table 2: Effect of oral administration of 10 mg/kg/day sitagliptin (Sita) for 7 weeks on the alterations induced by intraperitoneal (i.p.) administration of 60 mg/kg streptozotocin (STZ) and 110 mg/kg nicotinamide (NA) on the post-prandial blood glucose and HbA1c levels of STZ-NA diabetic rats.

Parameter	Treatment		
	Control	STZ-NA	Sita+STZ-NA
Post-prandial blood glucose (mg/dl)	212 ± 64	264 ± 66 **	119 ± 54 ^{##}
Glycosylated HbA1c (%)	3.03 ± 0.05	5.96 ± 0.05 *	3.18 ± 0.13 [#]

Blood samples were collected from tail vein after 8 weeks of induction of diabetes. Each value represents the mean ± S.E.M. of 8 observations, **Significant difference at $p < 0.01$ vs. control values. *Significant difference at $p < 0.05$ vs. control values. # Significant difference at $p < 0.05$ vs. STZ-NA values, ## Significant difference at $p < 0.01$ vs. STZ-NA values.

Effect of STZ-NA on kidney function parameters.

Serum urea level

As shown in figure 1, administration of 110 mg/kg NA and 60 mg/kg STZ i.p. showed a non-significant change in serum urea level after 4 weeks as compared to control rats. However, after 8 weeks of the same treatment,

serum urea level was significantly ($p < 0.01$) increased in comparison to control animals.

Serum creatinine level

Treatment of rats with 110 mg/kg NA and 60 mg/kg STZ resulted in a non-significant change after 4 weeks and a significant increase in serum creatinine ($p < 0.01$, Fig. 2) level after 8 weeks in comparison to control rats.

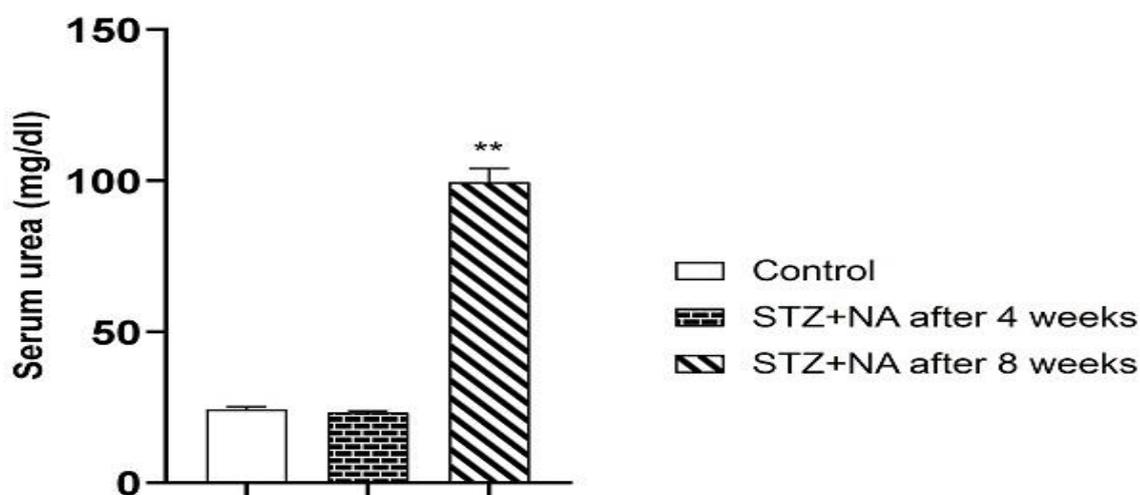


Fig. 1: Effect of intraperitoneal (i.p.) administration of 60 mg/kg streptozotocin (STZ) and 110 mg/kg nicotinamide (NA) to rats on serum urea levels. Blood samples were collected for biochemical measurements after 4 and 8 weeks of i.p. treatment of rats with STZ-NA. Each value represents the mean \pm S.E.M. of 8 observations. **Significant difference at $p < 0.01$ vs. control values.

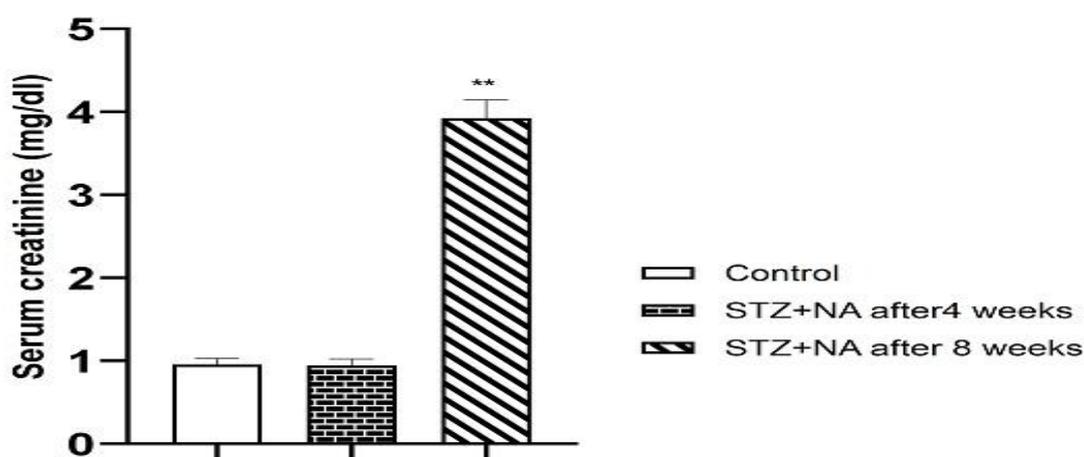


Fig. 2: Effect of intraperitoneal (i.p.) administration of 60 mg/kg streptozotocin (STZ) and 110 mg/kg nicotinamide (NA) to rats on serum creatinine level. Blood samples were collected for biochemical measurements after 4 and 8 weeks of i.p. treatment of rats with STZ-NA. Each value represents the mean \pm S.E.M. of 8 observations. **Significant difference at $p < 0.01$ vs. control values.

Urine albumin (Microalbuminuria)

After 4 weeks of treating rats with 110 mg/kg NA followed by 60 mg/kg STZ i.p., a non-significant change was observed in urine albumin (microalbuminuria) level. Additionally, the same treatment resulted after 8 weeks in a significant increase in urine albumin (microalbuminuria) level ($p < 0.01$, Fig. 3) as compared to control rats.

Results of the second set of experiments (sitagliptin treatment).

Effect of sitagliptin on fasting blood glucose level in STZ-NA diabetic rats.

Daily administration of 10 mg/kg sitagliptin orally for 7 weeks to STZ-NA diabetic rats produced a significant decrease in fasting blood glucose levels after 4 and 8 ($p < 0.01$, Table 3) weeks of induction of diabetes as compared to diabetic rats.

Effect of sitagliptin on post-prandial blood glucose and HbA1c levels in STZ-NA diabetic rats.

Administration of 10 mg/kg/day sitagliptin orally for 7 weeks to STZ-NA diabetic rats significantly decreased the post-prandial blood glucose level when measured 2 hours after breakfast ($p < 0.01$, Table 2) in comparison to diabetic rats.

Also, the same treatment of STZ-NA diabetic rats produced a significant decrease in HbA1c level ($p < 0.01$, Table 2) as compared to diabetic animals.

Effect of sitagliptin on kidney function parameters in STZ-NA diabetic rats.

Serum urea level

Administration of 10 mg/kg/day sitagliptin orally for 7 weeks to STZ-NA diabetic rats significantly decreased serum urea ($p < 0.01$, Fig. 4) level as compared to diabetic rats.

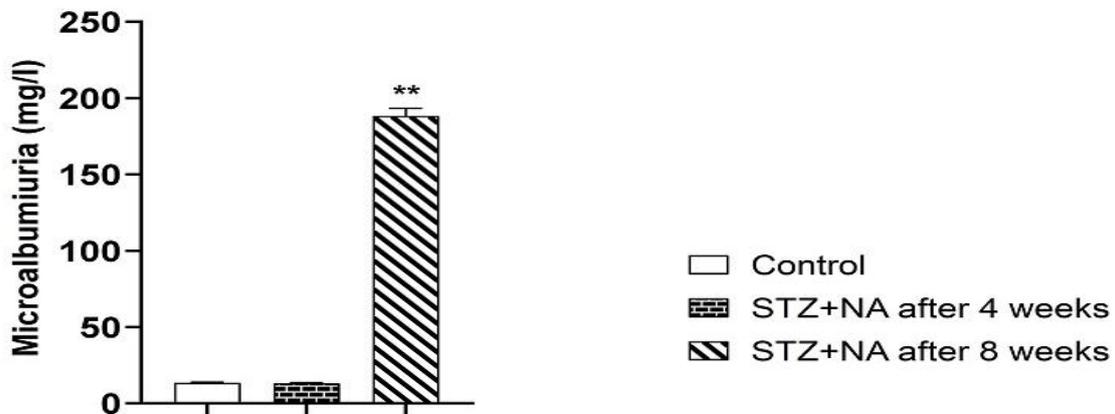


Fig. 3 Effect of intraperitoneal (i.p.) administration of 60 mg/kg streptozotocin (STZ) and 110 mg/kg nicotinamide (NA) to rats on urine albumin (microalbuminuria) level. Urine samples were collected for biochemical measurements after 4 and 8 weeks of i.p. treatment of rats with STZ-NA. Each value represents the mean \pm S.E.M. of 8 observations. **Significant difference at $p < 0.01$ vs. control values.

Table 3: Effect of oral administration of 10 mg/kg/day sitagliptin (Sita) for 7 weeks on fasting blood glucose level of diabetic rats.

Treatment	Time of measurement	
	After 4 weeks	After 8 weeks
Control	114.81 \pm 2.41	115.87 \pm 2.44
STZ-NA	532.92 \pm 14.99 **	561.61 \pm 19.29 **
Sita+ STZ-NA	239.90 \pm 9.45 ##	235.33 \pm 9.45 ##

Blood samples were collected from the tail vein after 4 and 8 weeks of induction of diabetes. Each value represents the mean \pm S.E.M. of 8 observations, **Significant difference at $p < 0.01$ vs. control values, ##Significant difference at $p < 0.01$ vs. STZ-NA values.

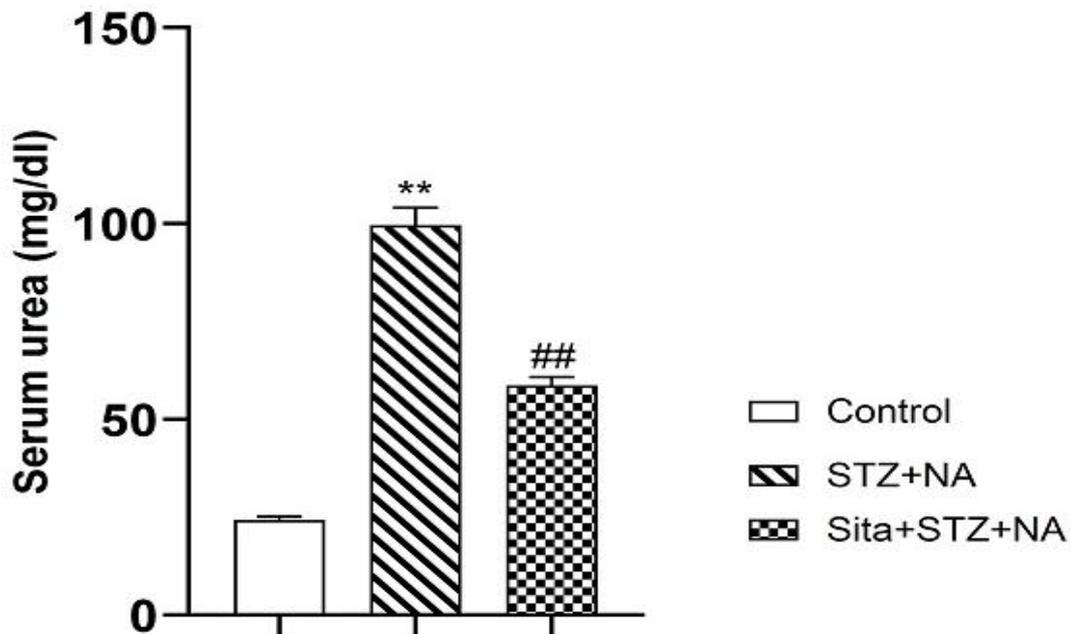


Fig. 4: Effect of treatment of diabetic rats with 10 mg/kg/day sitagliptin (Sita) orally for 7 weeks on serum urea level of diabetic rats. Blood samples were collected for biochemical measurements at the end of treatment duration. Each value represents the mean \pm S.E.M. of 8 observations. **Significant difference at $p < 0.01$ vs. control values. ## Significant difference at $p < 0.01$ vs. STZ-NA values.

Serum creatinine level

As shown in figure 5, administration of 10 mg/kg/day sitagliptin orally for 7 weeks to STZ-NA diabetic rats significantly decreased serum creatinine ($p < 0.01$) level as compared to diabetic rats .

Urine albumin (Microalbuminuria) level

Daily administration of 10 mg/kg sitagliptin orally to STZ-NA diabetic rats for 7 weeks significantly decreased urine albumin (microalbuminuria) ($p < 0.01$, Fig. 6) level in comparison to diabetic animals.

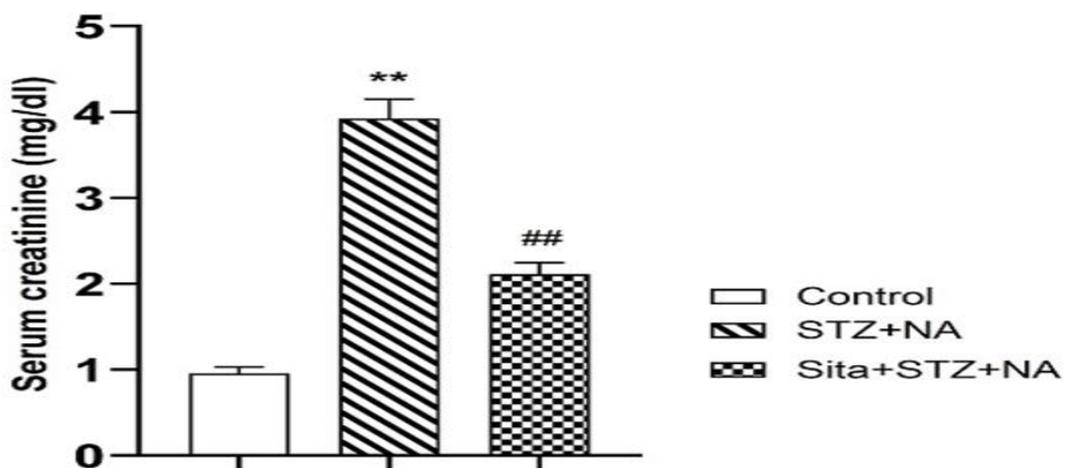


Fig. 5: Effect of treatment of diabetic rats with 10 mg/kg/day sitagliptin (Sita) orally for 7 weeks on serum creatinine level of diabetic rats. Blood samples were collected for biochemical measurements at the end of treatment duration. Each value represents the mean \pm S.E.M. of 8 observations. **Significant difference at $p < 0.01$ vs. control values. ##Significant difference at $p < 0.01$ vs. STZ-NA values.

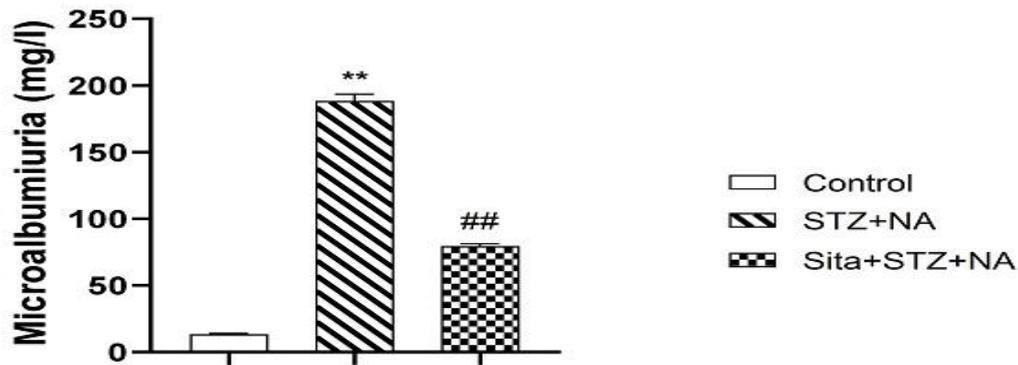


Fig. 6: Effect of treatment of diabetic rats with 10 mg/kg/day sitagliptin (Sita) orally for 7 weeks on urine albumin (microalbuminuria) level of diabetic rats. Urine samples were collected for biochemical measurements at the end of treatment duration. Each value represents the mean \pm S.E.M. of 8 observations. **Significant difference at $p < 0.01$ vs. control values. ##Significant difference at $p < 0.01$ vs. STZ-NA values.

Results of histopathological examination of kidney tissue

The histopathological examination of kidney tissue obtained after 4 weeks from rats treated with 110 mg/kg NA and 60 mg/kg STZ i.p. revealed no histopathological changes.

On the other hand, the histopathological examination of kidney tissue obtained after 8 weeks from rats treated with 110 mg/kg NA and 60 mg/kg STZ i.p. showed thickening of

the glomerular basement membrane, diffuse mesangial expansion, hypercellularity with formation of mesangial nodules, adhesions between glomerular tuft and parietal cells and lobulation of glomerular tuft. On the other hand, administration of 10 mg/kg/day sitagliptin orally to diabetic rats for 7 weeks showed mild thickening of the glomerular basement membrane and mild mesangial expansion (Fig.7 A, B and C).

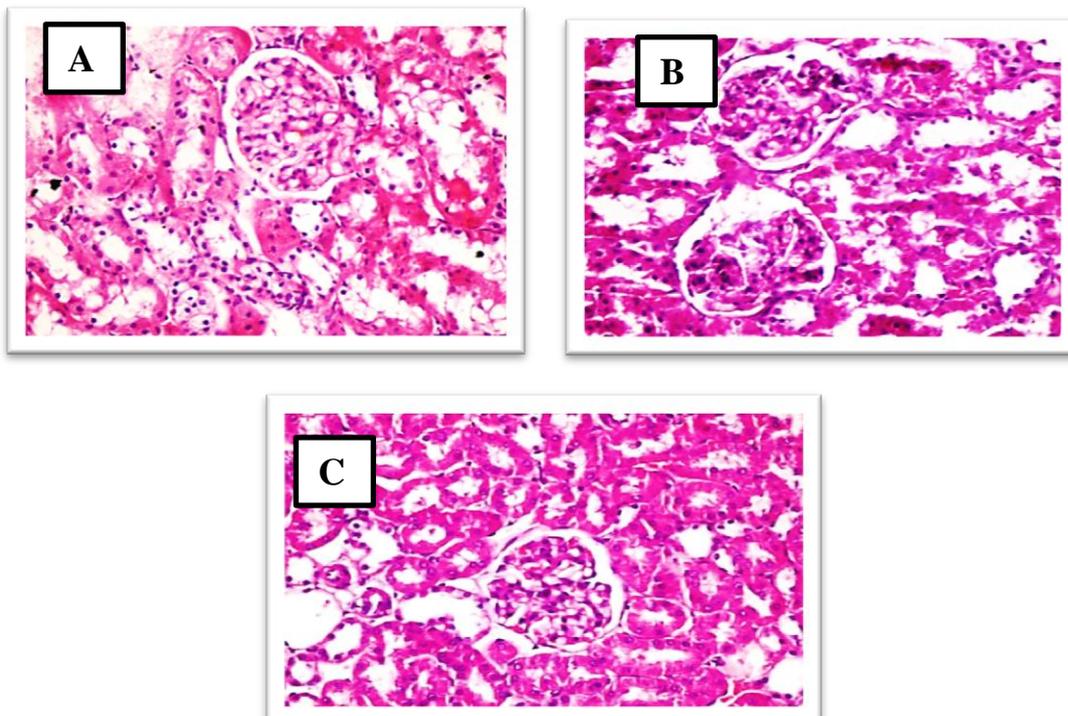


Fig. 7: Photomicrographs of representative kidney sections from **A:** control rats showing normal kidney tissue formed of normal glomeruli, tubules and interstitial tissues (H&E stain, x400), **B:** DN (STZ-NA) rats showing thickening of glomerular basement membranes, mesangial expansion and hypercellularity with formation of mesangial nodules and adhesions between glomerular tuft and parietal cells (H&E stain, x400), **C:** rats treated with sitagliptin (Sita) showing mild thickening of glomerular basement membrane and mild mesangial expansion (H&E stain, x400).

Discussion

A severe long-term microvascular consequence of T2DM is DN²⁸. A suitable and authorized animal model for the experimental induction of T2DM and DN is the combination of STZ and NA²⁵.

A naturally occurring glucosamine nitrosourea molecule known as streptozotocin (STZ) was first discovered as an antibiotic²⁹. After administration, it reaches the pancreatic cells quickly and breaks the DNA strands of the cells³⁰. Nicotinamide lessens the damage caused by STZ, which delays the onset of insulin insufficiency and mimics the symptoms of T2DM³¹. When blood glucose levels rise, glucose attaches to haemoglobin molecules in a concentration-dependent manner in diabetics. The relationship between HbA1c levels and blood glucose levels is important to note. As a result, as the average blood glucose levels rise, HbA1c levels rise as well³².

In the current study, the production of T2DM in rats resulted in a substantial increase in fasting blood glucose levels after 4 and 8 weeks as well as an increase in postprandial blood glucose and HbA1c levels after 8 weeks, as. These results are consistent with recent studies that found a significant rise in fasting and post-prandial blood glucose levels and HbA1c levels following STZ-NA injection^{33&34}.

The primary initiating factor linked to the ensuing cascades in the development of DN is hyperglycemia³⁵. Albuminuria and additional impairments in renal function are caused by chronic hyperglycemia. Albumin must traverse the three-part glomerular filtration structure, which is the main source of albuminuria. This three-part glomerular filtration structure is made up of three main cellular barriers; fenestrated glomerular endothelial cells, glomerular basement membrane (GBM), and glomerular epithelial cells or podocytes that are crucial for the ultrafiltration process. This three-layered structure is altered by metabolic disturbances brought on by hyperglycemia, such as increased intraglomerular pressure, loss of negatively charged glycosaminoglycans, and increased basement membrane pore size, which all contribute to albuminuria and further deterioration of the disease state³⁶. Early flattening and retraction of the podocytes' "foot processes" are linked to thickening of the GBM in diabetes. Initial microscopic findings include thickening of GBM, mesangial matrix growth, and an increase in the number of mesangial

cells³⁷. The earliest and most sensitive sign of impaired kidney function is microalbuminuria³⁸. Chronic hyperglycemia causes the glomerular filtration barrier to become less effective in conditions like DN, which increases albumin filtration into the urine (detectable microalbuminuria). These metabolic anomalies cause pathological glomerular alterations such mesangial enlargement and thickness of the GBM³⁸. Due to pore expansion and disruption of the GBM's electrical homeostasis, GBM damage increases albumin excretion³⁹.

Due to decreased glomerular filtration barrier function, DN is characterized by elevated serum levels of urea and creatinine, and microalbuminuria, which are crucial markers of DN³⁵. These findings, which showed a severe reduction in renal function following STZ-NA injection, are consistent with these observations. The considerable increase in serum urea, creatinine, and urine albumin excretion levels after 8 weeks indicated that function had been deteriorated. These renal functional traits point to the DN development⁴⁰.

Our histological findings in the kidney tissue after 8 weeks of STZ-NA administration further supported these biochemical changes in kidney function. The primary pathological changes in DN patients and animals include glomerular hypertrophy, excessive extracellular matrix accumulation, glomerular matrix expansion, thickening of the glomerular basement membrane, mesangial expansion, mesangial hypercellularity, tubular injury, and infiltration of inflammatory cells³⁵.

DPP-4 inhibitors, including sitagliptin, have been used more and more therapeutically in the therapy of T2DM. Insulin production and release from the pancreatic β - cells are subsequently stimulated as a result of sitagliptin's action on the DPP-4 enzyme in a manner that is reliant on glucose⁴¹. The direct effect of GLP-1 on pancreatic β -cells resulted in enhanced insulin levels and glucagon suppression, which tightly controlled the glyceic levels⁴².

Sitagliptin's favourable effects on the kidneys can be linked to significant glyceic control. Induction of proper blood glucose control may be one of the techniques used to reduce albuminuria. The reno-protective properties of sitagliptin may be attributed to its ability to lessen glucose fluctuations by

lowering postprandial and HbA1c levels as well as fasting blood glucose levels⁴³.

Our findings showed that sitagliptin medication effectively lowered both fasting and postprandial blood glucose and HbA1c levels. Additionally, sitagliptin prevented the decline in kidney structure and function, as seen by the decrease in serum urea and creatinine, and urine albumin levels (Microalbuminuria). Histopathological evidence further supported these biochemical advancements. Treatment with sitagliptin lessened the severity of renal histological changes brought on by STZ-NA, including GBM thickness and mesangial matrix growth. According to Marques et al.⁴⁴, sitagliptin enhanced kidney function, produced sufficient glycemic control, and alleviated tubulointerstitial glomerular lesions, all of which were findings that were supported by earlier research. Furthermore, according to clinical investigations^{45&46}, sitagliptin decreased albuminuria in many type 2 diabetes patients with nephropathy. According to Mega et al.⁴⁷, continuous sitagliptin treatment of an animal model of T2DM reversed glycemic dysmetabolism, lowered albuminuria, and lessened the severity of kidney tissue lesions on a histological level. Additionally, 16 weeks of treatment with low- or high-dose sitagliptin dramatically reduced serum urea and creatinine, urine albumin (microalbuminuria) levels in Wistar rats. The same sitagliptin therapy also led to improvements in glomerular lesions⁴⁸.

Conclusion

According to recent research, sitagliptin's ability to lower blood glucose levels and its improvement of kidney structure and function deficiencies allowed rats with STZ-NA-induced diabetes to have better kidney function and slow the advancement of DN. In order to slow the development of DN, sitagliptin appears to be a promising therapeutic approach for the treatment of diabetes mellitus. To investigate the favourable effects of sitagliptin as a DPP-4 inhibitor in the prevention of diabetes macrovascular and microvascular problems and to identify new mechanisms of action, additional experimental and clinical trials are advised.

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نشرة العلوم الصيدلانية جامعة أسيوط



التأثير المعدل المحتمل لمثبط الداى بيبتيديل بيبتيدياز-٤، سيتاجلبتن على اعتلال الكلية السكري الناجم عن الستربتوزوتوسين-نيكوتيناميد في الفئران

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يعتبر اعتلال الكلية السكري من المضاعفات الرئيسية لمرض السكري الذي يسبب مرض الكلى في المرحلة النهائية. ارتفاع السكر في الدم هو عامل خطر رئيسي متورط في بدء وتطور الاعتلال الكلوي. هدفت دراستنا إلى تقييم التأثير الوقائي للسيتاجلبتين في الاعتلال الكلوي الناجم عن الستربتوزوتوسين-نيكوتيناميد في الفئران. ولقد استحدثنا الاعتلال الكلوي في الفئران بعد ثمانية أسابيع من حقن الستربتوزوتوسين-نيكوتيناميد في منطقة الصفاق. وتم قياس مستويات السكر في الدم (صائم) و بعد الأكل بساعتين ونسبة الهيموجلوبين السكري بالإضافة إلى قياس مستويات اليوريا والكرياتينين في الدم الزلال في البول وذلك في مجموعة الجرذان المصابة بالاعتلال الكلوي ومجموعة الجرذان المصابة بالاعتلال الكلوي ومجموعة الجرذان المصابة بالاعتلال الكلوي والمعالجة بالسيتاجلبتن. تم إجراء تقييم الأنسجة المرضية لأقسام الكلى المضمنة بالبارافين. قلل السيتاجلبتن من مستويات السكر المرتفعة في الدم (صائم) و بعد الأكل بساعتين ومستويات الهيموجلوبين السكري. بينما عكس السيتاجلبتن التغييرات التي سببها الستربتوزوتوسين-نيكوتيناميد في وظائف الكلى وهيكلها. تشير النتائج إلى أنه يمكن منع الاعتلال الكلوي بواسطة السيتاجلبتن عن طريق التحكم الصارم في نسبة السكر في الدم، مما يحسن وظائف الكلى المتدهورة ويحفظ البنية الكلوية.